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– CASE REPORTS –

Chronic Myeloid Leukemia Presenting with Megakaryocytic Blast Crisis: a Case Report with a Favorable Outcome

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Abstract

Chronic myeloid leukemia (CML) belongs to the chronic myeloproliferative neoplasms, a clonal disorder of pluripotent hematopoietic stem cells, arising because of a hallmark genetic anomaly- reciprocal translocation between chromosomes 9 and 22, known as the Philadelphia chromosome, which generates the BCR::ABL fusion gene. The disease can have a biphasic/triphasic evolution, comprised of an accelerated phase and a terminal blast phase (usually biphasic when blastic phase is lymphoid in nature). Most cases present during the chronic phase of the disease, with only 10% of cases presenting in the blast phase. Megakaryocytic blast crisis is an unusual form of presentation, accounting for less than 3% of cases and it commonly carries an unfavorable prognosis compared to the classic myeloid, lymphoid or even mixed lineage blast crises. Aim: To bring forth an unusual case of CML presenting with megakaryocytic blast crisis and the therapeutic challenges associated with this particular presentation, unexpectedly ending with a favorable outcome. Matherial and methods: we hereby present the case of a 50 year old female patient, diagnosed in 2015 with CML- megakaryocytic blast crisis, who underwent treatment with a tyrosine kinase inhibitor (TKI)- imatinib and intensive chemotherapy regimen 3+7, without satisfactory response. A second induction chemotherapy regimen followed (MEC), alltogether with the same TKI and cytoreductive treatment (hydroxyurea/HU), but still without achieving a complete remission. Thus, the TKI was switched to dasatinib and complete normalisation of blood counts followed (including thrombocytes). However, there was still inadequate molecular and cytogenetic response. Therefore, TKI dosage was increased and after 4 months the patient achieved complete remission, with no detectable BCR::ABL transcript. She spent 9 years on the same TKI until important pleural effusion developed, which required switching to another 2nd generation TKI- bosutinib, based on the patients age, genetic profile and commorbidities. She is still in complete remission without detectable BCR::ABL transcript/Philadelphia chromosome to this day (2024). Results and conclusions: this is the case of a rare presentation of CML- megakaryocytic blast crisis, who underwent both TKI and intensive chemotherapy induction regimens, marked by a favorable unexpected outcome.

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Case Report

A 50 year old female, with a history of bronchial asthma and no other known commorbidities, without remarkable familial medical history and no apparent exposure to toxic environment, presents in february 2015 with anemia related symptoms (mostly fatigue and heart palpitations) and abdominal fullness accompanied by tenderness in the left upper quadrant. The symptoms had a 2 months evolution pattern. Clinical examination revealed important hepatosplenomegaly and mucocutaneous palor. Laboratory work-up showed a full blood count (FBC) with normocytic normochromic anemia (haemoglobin 9 g/dl), marked leukocytosis (77.000/mm3) with neutrophilia (33%), basophilia (17%) and thrombocytosis (597.000/mm3). Peripheral blood smear (PBS) was obtained, which showed 50% polymorphic myeloid blasts, large dysmorphic thrombocytes, frequent megakaryocytes and megakaryoblasts, giant erythrocytes and erythroblasts.

Naturally, a bone marrow examination followed, through a bone marrow aspiration procedure, which revealed the following aspect: hypercellular marrow, with a hypercellular granulocytic lineage, left deviation of neutrophil maturation pattern and also left deviation of basophil maturation pattern, with notable basophilia and presence of basophilic precursors, eosinophilia, frequent myeloid blast cells (31%) and undifferentiated blast cells; hypocellular erithroid lineage, abundant megakaryocytic lineage, with frequent megakaryocytic islets, micromegakaryocytes and megakaryoblasts, frequent cellular elements with asynchronous development and dysmorphic aspect; conclusion- blast phase of a chronic myeloid leukemia with basophilia, possibly megakaryocytic blast crisis/ AML M7.

Cytogenetics analysis revealed an unconclusive result, but molecular biology came to the rescue, showing 100% positivity for BCR::ABL (p210) transcript. Additionally, we tested for JAK2V617F mutation, but it came back negative.

The patient refused undergoing a bone marrow biopsy procedure and any subsequent bone marrow examination procedures at first. Thus, peripheral blood flow cytometry followed, showing these results (fig.1, fig.2):

- 19% precursors, 17% basophils, 33% neutrophils, 5% eosinophils, 4% lymphocytes, 20% CD45- cells;
- 27% CD34+ blasts (68% in the CD45+ precursor region and 32% in the CD45- region);
- in the CD45+ dim/SSlow precursor region, the following phenotypic features were identified:
  - 80%: CD33+, CD34+; 89%: CD34+, HLADR+; 91%: CD38+; 95%: CD71+; 9%: MPO+.
  - Negative for CD117, CD11b, CD15, CD16, CD14, CD56, CD36, CD123, CD19, CD7.
- the selected basophils in the CD45+mod/SSlow region carried the following phenotype:
  - 99%: CD33+; 94%: CD13+; 88%: CD123+ HLADR-; 89%: CD123+ CD38+; 89%: CD9+; 73%: CD25+dim.
  - Negative for MPO, CD34, CD117, CD14, CD56, CD36, CD64, CD19, CD7.

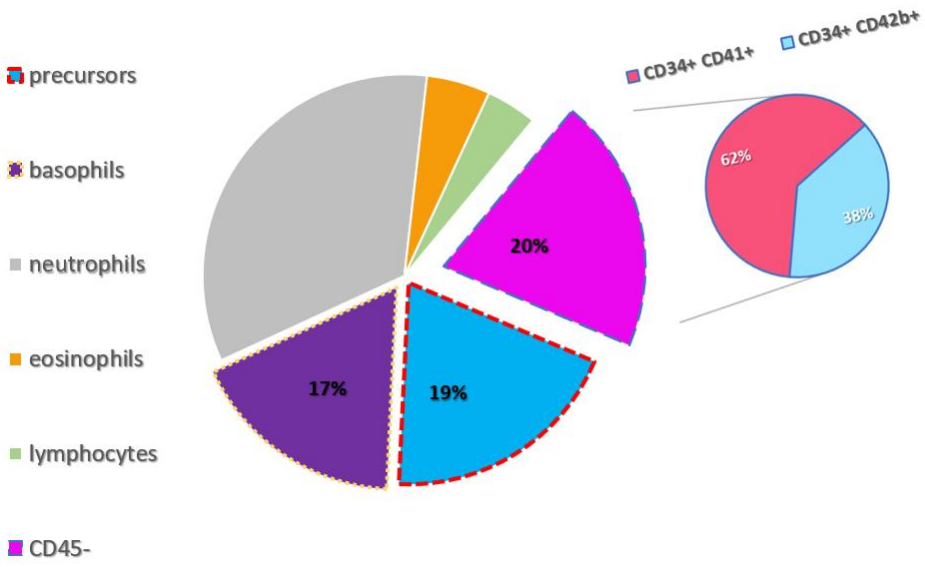

Figure 1. Summary of flow cytometry plots and results at diagnosis

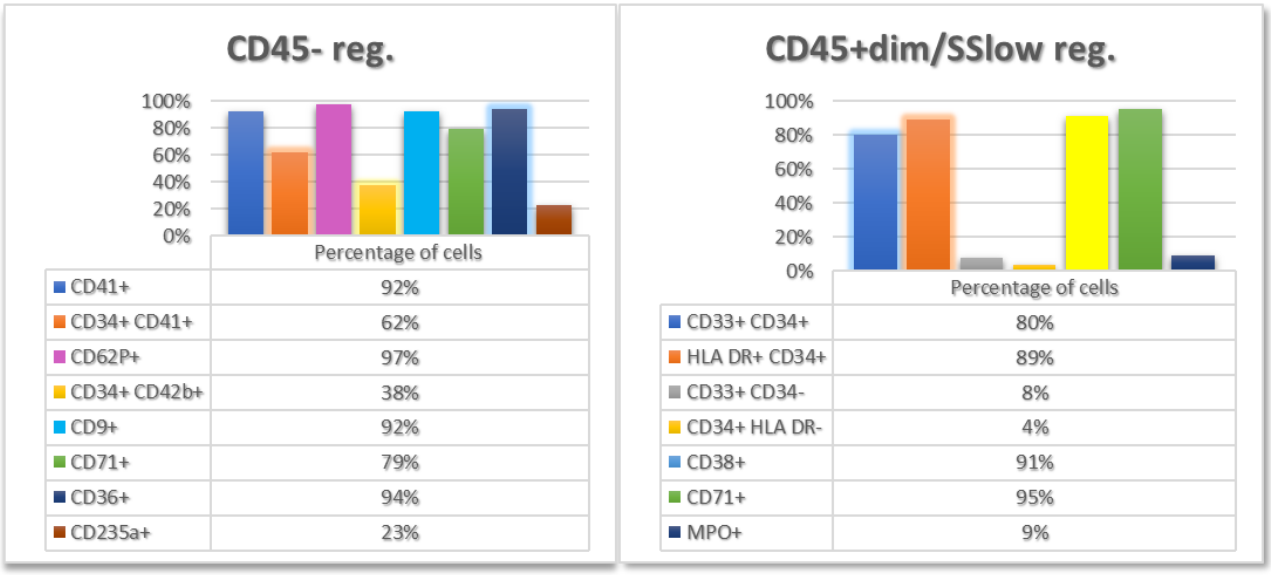

Figure 2. Representation of flow cytometry phenotypes- cell population analysis

- the selected neutrophils in the CD45+mod region carried the following phenotype:
  - o 92%: MPO+; 99%: CD33+; 90%: CD13+; 97%: CD15+; 80%: CD11b+; 44%: CD64+.
  - o Negative for CD7, CD19, CD56.
  - o 16% mature neutrophils CD16+, hypogranular.
- in the CD45- region the following phenotypic features were identified:
  - o 92%: CD41+; 62%: CD34+, CD41+; 97%: CD62P+; 38%: CD34+, CD42b+; 92%: CD9+; 79%: CD71+; 94%: CD36+; 23%: CD235a+.
  - o Negative for CD13, CD33, MPO, HLADR, CD64.

Therefore, flow cytometry concluded the following diagnosis: CML- blast crisis with megakaryocytic and myeloid precursors/ AML M7.

Biochemistry work-up revealed elevated LDH (3762 u/l) and moderate elevation of systemic inflamation markers. Viral screening came back negative for HIV, hepatitis B and C viruses.

An abdominal ultrasound was performed, showing an enlarged liver in close contact with the spleen (left lobe 7.6 cm, right lobe 17.5 cm) and severe splenomegaly (long axis > 22 cm, with the inferior pole situated under the umbilical region).

Cardiac ultrasound revealed normal ejection fraction (EF 70%) without additional anomalies, normal left ventricle contraction pattern.

Given the disease presentation, the patient was submitted to counseling regarding the need of undergoing hematopoietic stem cell transplantation (HSCT) in the near future. We proceeded to HLA compatibility testing. The patient had 6/6 HLA (2 digits testing) compatibility with a first-degree relative (sister), with the subsequent 4 digits testing planned to take place after the approval of the regional Transplant Committee. However, the patient refused undergoing preparation for the HSCT procedure and the procedure itself.

A specific induction chemotherapy protocol was started, consisting of a 3+7 regimen type (cytarabine and doxorubicin) along with a TKI- imatinib and supportive therapy. Complications arised in the +8th day after chemotherapy, comprised of fever, dysphagia and odynophagia, with negative blood cultures and negative pharyngeal exudates. Antibiotherapy followed, initially with fluoroquinolones (moxifloxacin) and sulphonamides (sulfamethoxazole/trimethoprim), with HHC and antipyretics; persistence of febrile syndrome prompted escalation to carbapenems (imipenem/cilastatin), which resulted in remission of fever and symptoms.

The clinical evolution was initially favorable: spleen size normalised (12.8 cm long axis) and blood counts dropped to normal values (leukocytes), however persistent severe thrombocytosis was observed (1048 x 103/µL). Bone marrow evaluation showed normocellular marrow, yet frequent islets comprised of thrombocytes; thrombogenic megakaryocytes were present, together with rare undifferentiated blasts, normoblastic eritropoiesis,

granulocytic lineage with maturation, thus emphasizing once again megakaryocytic hyperplasia.

Flow cytometry, performed from bone marrow aspirate sample this time, showed 36% precursor cells (with variable CD45 expression), 30% granulocytes, 11% lymphocytes, 2% monocytes, 1% basophils, 18% erythroid cells; 33% CD45- precursor cells, with the following phenotype: CD34+, CD41+, CD42b+, CD9+, CD36+, CD117+dim; negative for HLADR, CD33, CD13, CD7, CD123, CD71, CD235a. The identified phenotype was compatible with AML M7/acute megakaryocytic leukemia.

These results prompted the administration of another chemotherapy induction regimen, starting March 2015 – MEC (mitoxantrone, etoposide, cytarabine), TKI- imatinib, cytoreductive agents- HU, antiplatelet medication- aspirine, along with supportive therapy (antiemetics, xanthine oxidase inhibitors to limit uric acid production, prophylactic antibiotherapy- FQ and antifungals). Once again, the patient developed fever, odynophagia and dysphagia, in the +8th day after chemotherapy. Urine culture showed presence of Klebsiella spp. Therefore, prophylactic therapy is escalated- administration of intravenous antifungals, antibiotherapy with imipenem/cilastatin, levofloxacin, followed by the addition of teicoplanin and colistin. However, in the +13th day, fever returns, with negative blood cultures and with a radiographic appearance compatible with bilateral pneumonia, which prompts escalation of therapy to voriconazole, tigecycline, colistin, amikacin, trimethoprim/sulfamethoxazole, acyclovir, in conjunction with granulocyte colony stimulating factor. Patient's evolution was favorable eventually but unfortunately, complete remission was not obtained- persistence of thrombocytosis was still observed. Thus, we switched towards a 2nd generation TKI- dasatinib, but kept cytoreductive treatment (HU).

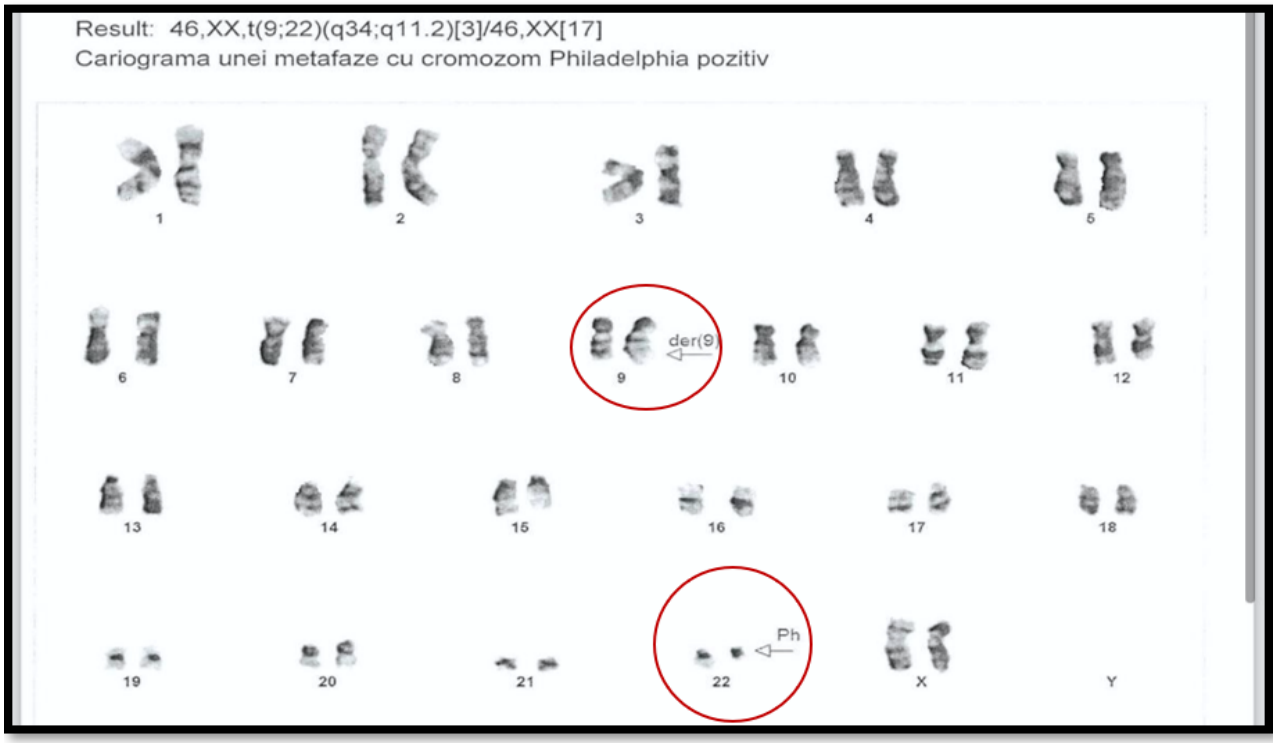

Figure 3. Courtesy of Personal Genetics Laboratory (Medical Genetics Centre) Bucharest, classic cyteogenetics, positive Ph. chromosome karyogram during treatment.

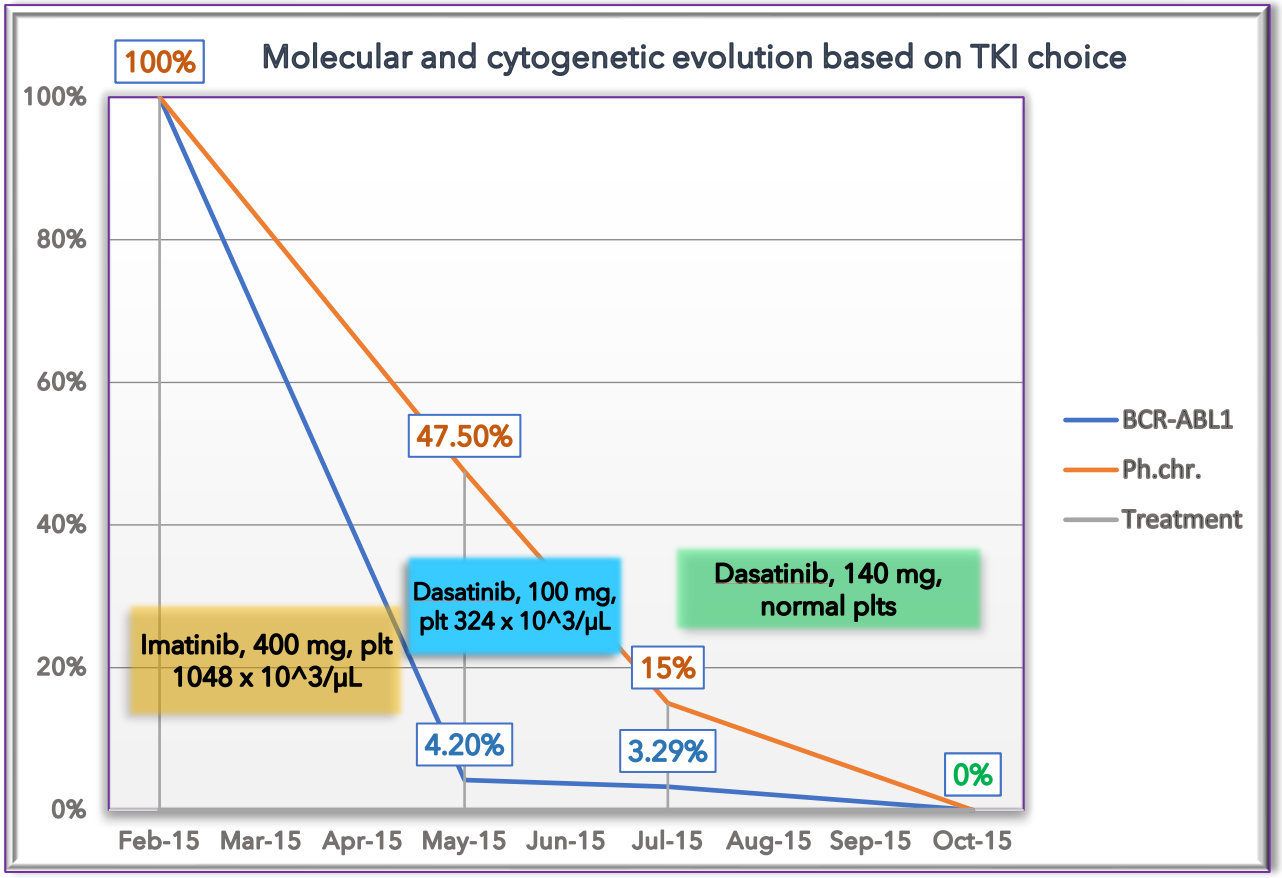

Figure 4. Molecular and cytogenetic evolution based on TKI choice- from first induction to final complete remission, Feb 2015-Oct 2015; plt/plts- platelets; Ph.chr.- Philadelphia chromosome.

May 2015 brought a temporary severe aplasia following treatment, with normalisation of thrombocytes numbers, but severe leucopenia and anemia emerged. Molecular exam showed 4.2% BCR- ABL, cytogenetics- 47.5% Philadelphia chromosome positive cells. Bone marrow flow cytometry revealed hypocellular sample, with 3% myeloblasts, 3% cells belonging to the megakaryocytic lineage and 19% eosinophils. Bone marrow morphology completed the previous described results, once again confirming marrow aplasia. In order to thoroughly assess the evolution of the disease, we also performed a bone marrow biopsy which showed the same results.

An abdominal ultrasound was performed, showing spleen size 11.2 cm and cardiac ultrasound showed normal left ventricle function, with EF 60%. We concluded the patient's complete hematological remission (based on the results of the aforementioned investigations- bone marrow biopsy, flow cytometry and morphology), however there was no satisfactory molecular and cytogenetic response. Consequently, dasatinib dosage was increased.

July 2015 showed improved molecular and cytogenetic response: 3.29% BCR-ABL and 15% Philadelphia chromosome positive cells, without other numerical or structural anomalies (i.e. without additional chromosomal anomalies/ACA; fig.3). We also tested for the presence of mutations associated with TKI resistance and the panel came back negative. The subsequent bone marrow biopsy showed unspecific aspect, with features compatible with recovery after treatment (regenerative aspect of BM).

October 2015 brought complete treatment success with undetectable BCR-ABL transcript and no Philadelphia chromosome positive cells. The succeeding molecular and cytogenetic evaluations showed complete remission. The patient consistently refused undergoing preparation for HSCT and the procedure itself (fig.4 and fig.5).

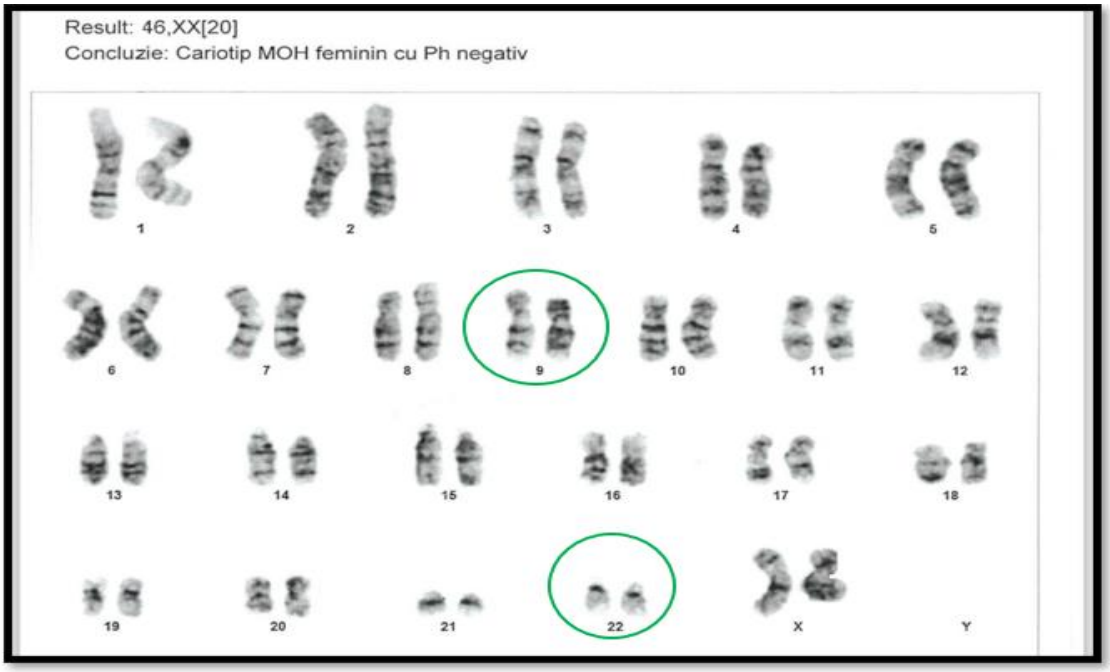

Figure 5. Courtesy of Personal Genetics Laboratory (Medical Genetics Centre) Bucharest, classic cytogenetics, negative Ph. chromosome karyogram, after TKI switch and increased dosage

Dasatinib treatment was well tolerated for almost 9 years, until the patient developed important pleural effusion (June 2023) and was referred to a thoracic surgery department, for removal and analysis of pleural fluid. Of important notice- a pleural biopsy was also performed. There were no atypical cells identified, only lymphocytes, monocytes and reactive mesothelial hyperplasia. As a result, we considered this to be a late adverse reaction to dasatinib; we switched to another 2nd generation TKI- bosutinib, given the patient's age and commorbidities' status- the patient developed angina and underwent multiple cardiac evaluations, however without requiring hospitalisation.

To this day, the patient's laboratory work-up (including molecular and cytogenetic exams) show complete remission, with good adherence and tolerance regarding bosutinib.

Discussions

CML represents a common myeloproliferative neoplasia, characterised by its genetic hallmark- the Philadelphia chromosome, which leads to the creation of BCR::ABL fusion gene. It can be associated with ACA and other molecular secondary changes. The unique product formed through the process of reciprocal translocation between chromosomes 9 and 22, the BCR-ABL1 fusion protein, includes an enzymatic domain, with constitutive elevated kinase activity, which is mostly disregulated. Thus, clinically, CML is characterised by the uncontrolled production of granulocytes (both mature and maturing ones), usually neutrophils, but eosinophilia and basophilia are a frequent finding and also, the latter, a hallmark of myeloproliferation. In the absence of treatment, the disease has a biphasic or triphasic evolution, as it can progress from a chronic phase to an accelerated phase and eventually, it can reach a terminal, blast phase. If the blast phase is lymphoid in nature, there is usually no accelerated phase. (1), (2), (3), (4)

In what concerns clinical manifestations, 20-50% of patients can be asymptomatic, the disease being discovered during routine blood tests. However, fatigue, excessive sweating, abdominal fullness and left upper quadrant tenderness and pain (splenomegaly) alltogether with bleeding episodes and even weight loss can be encountered. (2)

Regarding the PBS and FBC, leukocytosis with proliferation of granulocytes are abundant features- from myeloblasts to mature neutrophils, with blasts usually less than 2%; basophilia is a universal finding. Proeminent monocytosis can be found in those who carry another breaking point in chromosome 22, giving rise to a p190 BCR-ABL1 fusion protein. (2)

Platelet counts can be normal or elevated, however thrombocytosis can be seen in 15-30% of patients. Anemia can be another common feature, usually normochromic and normocytic. (2), (5)

Most of the patients are mainly diagnosed during the chronic phase of the disease, with few actually diagnosed during overt blast crisis. Attempting to foresee progression to blast crisis is a difficult task, with many factors involved still being under intense research. It is generally thought that accumulating different various mutations and subsequently developing ACA can lead to further advancement to blast crisis. (1), (6)

The first time acute megakaryocytic leukemia was described, was in the 1930s, when the presence of blast cells with similar morphology to that of megakaryocytes was observed (blasts with cytoplasmic blebs, intense basophilic cytoplasm, etc). What we today identify as the FAB AML M7 entity, was created as an entity in 1985, when specific diagnostic criteria was established through specific cytochemical staining, such as platelet peroxidase, by electron microscopy (which proved the megakaryocytic lineage origin of blasts). The presence of specific MK antigens determined by flow cytometry (positivity for CD41, CD42, CD61, factor VIII antigen) was later added. Extensive fibrosis is usually present and this affliction was once reffered to as acute myelofibrosis (with panmyelosis). On that note, blasts in acute myelofibrosis lack MK differentiation (or if present, not significant). Also, there is marked cytogenetic variability regarding the encountered anomalies- either trisomy of chromosomes 21 and 8, or anomalies of chromosomes 5 or 7. (7), (8), (9).

CML presenting with megakaryocytic blast crisis is extremely rare, with few cases reported worldwide. Usually, blast crisis can be myeloid or lymphoid in nature. The majority of CML with megakaryocytic blast crisis reported cases are those of patients with previously diagnosed CML, usually already under treatment with a TKI (most commonly- imatinib) who underwent transformation along the way, and even so- it is still a rare occurrence, with less than 3% of transformed cases. Prognosis is usually unfavorable, and the majority of available case reports have shown unfortunate cases with rapid disease progression, treatment resistance and exitus. Other case reports have focused mostly on diagnosis and differential diagnosis criteria and key points, given the difficulty of establishing and differentiating between de novo acute megakaryocytic leukemia (AML M7) and CML with megakaryocytic blast crisis. Once again, cytogenetics and flow cytometry are essential vital tools and without their availability, the chance to actually provide adequate diagnosis and treatment drops extremely low. (10), (11)

Differential diagnosis between de novo AML M7 and CML in blast MK crisis is usually based on clinical presentation, accompanied and certified by bone marrow morphology evaluation, bone marrow biopsy, flow cytometry and cytogenetic exams. De novo AML M7 would normally lack positivity for BCR-ABL and the Philadelphia chromosome (although there have been some case reports of Philadelphia chromosome positive AML). Also, severe hepatosplenomegaly, alltogether with FBC demonstrating marked leukocytosis and basophilia, stand for CML. If the PBS or BM aspirate demonstrate presence of at least 20% blasts or if there is extramedullary blast infiltration, we can definitely conclude the existence of a blast crisis (WHO criteria). This is also the case regarding our patient, who presented with marked hepatosplenomegaly and FBC aspect that clearly indicates a previous chronic myeloproliferative process, specifically CML. The PBS and BM examination confirmed the blast crisis. Flow cytometry showed positivity for specific megakaryocytic lineage antigens and molecular biology confirmed presence of BCR-ABL1 fusion product. (8), (12), (13), (14)

Regarding flow cytometry, having adequate reactives and access to specific megakaryocytic antibodies is crucial in order to firmly assess the suspected diagnosis. There are few case reports limited in credibility because of the lack of specific reactives to thoroughly assess the presence of specific MK lineage antigens, given the fact that there can also be intense positivity for common myeloid markers alltogether with markers of immaturity, thus differentiating between a common myeloid blast crisis and a MK one being extremely difficult. (8), (12), (15), (16), (17)

Another distinct aspect between de novo AML M7 and CML in MK blast crisis would be thrombocytosis. Usually, CML in MK blast crisis presents with normal platelets or even important thrombocytosis, whereas de novo AML M7 presents commonly with thrombocytopenia and sometimes, pancytopenia. (12), (18)

What sometimes renders difficulty in evaluating the course of the disease is the bone marrow fibrosis associated with MK crisis presentation (it has been proven that megakaryocytes stimulate fibroblasts, by activating factors capable of activating fibroblastic precursors). (18)

With reference to the treatment choice, there is general consensus that chemotherapy regimens based on mitoxantrone and etoposide have shown promising hematological response next to the classical 3+7 type regimens. Regarding the TKI choice as initial therapy in such cases, there is a lack of data, probably because there is a scarcity of case reports which such a presentation of

blast crisis and there aren't many available studies on large cohorts of pacients with this specific form of presentation. Given the time when the patient was diagnosed, first choice of therapy was generally considered TKI/imatinib plus AML type induction chemotherapy, 2nd generation TKIs being set aside as a back-up resort in case there was inadequate response to the first attempted choice of treatment. There are case reports with favorable hematological response to imatinib and AML type induction chemotherapy, however with no satisfactory cytogenetic and molecular response (persistence of Philadelphia chromosome and BCR-ABL1 fusion protein). Some data suggest following treatment with TKI alone and then proceeding to HSCT, even though there is no final consensus regarding which TKI is optimal as first line treatment in such cases; however, current data suggest starting with a second generation TKI. (19), (20), (21), (22)

Returning to our current case, after first induction regimen (3+7 type) and imatinib, the patient went through favorable clinical evolution, with spleen and liver size normalisation and also normalisation of white blood cell counts; however, there was persistent thrombocytosis, with progressive severity, reaching 1048 x 103/µL. Subsequent evaluations of bone marrow aspirate and second flow cytometry showed AML M7 aspect. Second induction regimen-MEC, didn't achieve remission, even though additional cytoreductive treatment was included (HU). Only after imatinib was switched for a 2nd generation TKI- dasatinib, we managed to achieve complete hematological remission with the normalisation of platelet counts, followed, a few months after, by complete cytogenetic and molecular remission.

Considering the current case carried a high risk score and an adverse prognosis, a higher dosage of dasatinib would have been the ideal choice to start with since the beginning. However, given the financial burden associated, the limited availability of the drug at the time of diagnosis and the scarcity of reported data regarding this specific presentation, we directed our view towards imatinib, a 1st generation TKI, combined with chemotherapy induction regimen.

Recent case reports favor as treatment, once a clear diagnosis of CML in MK blast crisis has been made, 3+7 induction chemotherapy regimen and dasatinib- with favorable results. Nevertheless, it is generally stated that allogeneic HCT is the treatment of choice once conversion to chronic phase is achieved, given the fact that TKIs haven't been proven to offer long-term survival certainty. Our patient refused undergoing HSCT, even though she had a compatible available related donor, suprisingly still harboring complete remission after almost 9 years. The only reason that prompted the switch to another 2nd generation TKI was intolerance to dasatinib by developing important pleural effusion. Of important note, the subsequent molecular exams showed no detectable BCR-ABL1. (12), (20)

Compared to other case reports available, we still managed to achieve complete clinical, hematological, molecular and cytogenetic remission. It should be noted that each time we performed regular cytogenetic exams, there were no additional chromosomal anomalies encountered (either structural or numerical) and T315I mutation was negative, unlike other case reports available- which mentionted either presence of ACA during disease evolution or T315I positivity. (3), (4)

Whether this case's succes stands on purely incidental positive occurence or on much more complex unknown mechanisms, remains to be seen.

Abbreviation list

ACA- additional chromosomal anomalies
AML M7- acute megakaryocytic leukemia
AML- acute myeloid leukemia
BM- bone marrow
CML- chronic myeloid leukemia
FBC- full blood count
FQ- fluoroquinolones
HHC- hydrocortisone hemissuccinate
HSCT- hemtopoietic stem cell transplant
HU- hydroxyurea
LDH- lactate dehydrogenase
MEC- mitoxantrone, etoposide, cytarabine
MK- megakaryoblastic/megakaryocytic
PBS- peripheral blood smear
TKI- tyrosine kinase inhibitor
WHO- World Health Organization

No funding for this study

Conflicts of interest

I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work. The authors declare no conflict of interest.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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