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– ORIGINAL PAPERS –

Chronic Myeloid Leukemia: From the Classical Presentation Towards Rare Instances of Associated Blast Crises - Case Comparison and Literature Review

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Abstract

Chronic myeloid leukemia/CML accounts up to 20% of leukemia cases in the adult population. Even though the TKI (tyrosine kinase inhibitors) era has brought major improvements regarding evolution and prognosis, there are still certain particularities encountered in clinical practice concerning disease presentation, that can alter its evolution and the therapeutic approaches. Aim: to emphasize the diagnostic and therapeutic particularities of 3 CML cases, going from a classical form of presentation to rare instances- extremedullary lymphoid blast crisis (parasternal subcutaneous mass) and megakariocytic blast crisis. Methods: Pacient M.C., aged 25 years old, presents with hyperleukocytosis, moderate anemia and severe heptosplenomegaly; laboratory work-up showed chronic phase CML. By comparison, pacient H.I, aged 33 years old presents with similar clinical picture; laboratory work-up showed chronic phase CML. However, during clinical examination, a small parasternal mass was observed and a biopsy was performed which revealed extramedullary lymphoid blast crisis. Pacient Z.M, aged 50 years old, presents with leukocytosis, mild anemia and moderate thrombocytosis, adding to the clinical picture a severe hepatosplenomegaly. Additional laboratory work-up confirms CML with megakariocytic blast crisis. Results: different therapy protocols were applied- TKI, acute lymphoblastic leukemia protocols and acute myeloid leukemia induction regimen associated to TKIs, with favorable outcomes. Conclusions: rare CML presentation forms should not be dismissed, given the important differences brought by diverse therapeutic protocols regarding the same disease, carring great influence on prognosis and survival.

Keywords: *chronic myeloid leukemia, blast crisis, TKI, BCR-ABL, chemotherapy, myeloproliferative disease*

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Series of Cases. Case Comparison

A 25 y.o. female, M.C, without any remarkable medical history, presents in august 2023 with marked asthenia, vertiginous syndrome and important splenomegaly (10 cm under costal margin). Laboratory work-up revealed hyperleukocytosis (292 000/cmm), with neutrophilia (243 000/cmm), important basophilia (18 000/cmm) and thrombocytosis (434 000/cmm), mild normocytic normochromic anemia (Hb 9.3 g/dl). The peripheral blood smear (PBS) showed left-shifted deviation of leukocytes up to 4% blasts, with all granulocytic lineage maturation forms present. A bone marrow aspirate was performed, showing granulocytic lineage hyperplasia with left-shifted myeloid maturation and 2% myeloblasts. Additionally, we tried performing a cytogenetics exam, however there was no possibility of adequate aspirate extraction due to dry tap. Consequently, a bone marrow biopsy followed, confirming the diagnosis- chronic myeloproliferative neoplasia, chronic myeloid leukemia in chronic phase. Molecular biology completed the clinical and paraclinical picture- positive for BCR-ABL1 transcript 85% (b2a2/b3a2, p210). We continued with routine investigations such as abdominal ultrasound which revealed hepatosplenomegaly (spleen size 23 cm and liver size right lobe 19 cm).

Treatment approach consisted of introducing a 2nd generation tyrosine-kinase inhibitor (TKI), dasatinib, with favourable response and without major adverse events- major molecular response/MMR undetectable BCR-ABL1 12 months after and still in remission to this day. Applied risk scores consisted of Sokal score- 1 pt, intermediary risk, Hasford score 1105 pts, intermediary risk, and EUTOS/ELTS- 1.67 pts, intermediary risk. These scores shaped and supported therapy choice.

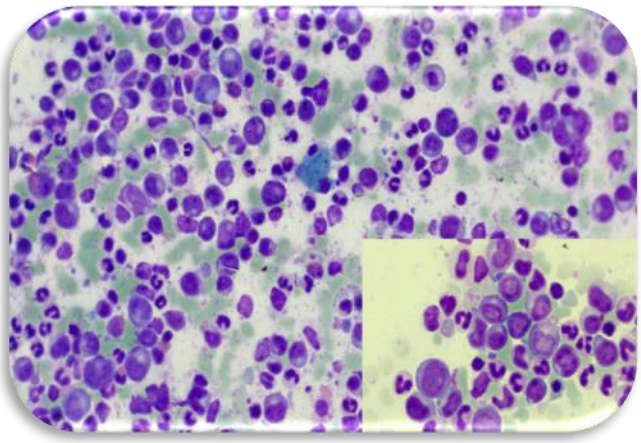

Figure 1. *♀ M.C. Bone marrow aspirate, 40x, Giemsa; chronic myeloid leukemia aspect: left-shifted deviation of granulocytic lineage up to myelocytes, immature basophils and sea blue histiocyte - courtesy of Hematology Laboratory of Colțea Clinical Hospital.*

Going further, a second case, clinically similar to the previous one at first glance, a young 33 y.o male, H.I., without remarkable medical history, presents in september 2021, with excessive fatigue and sweating. Laboratory work-up showed similar hyperleukocytosis (200 000/cmm), neutrophilia (167 000/cmm), monocytosis (11 000/cmm), thrombocytosis (570 000/cmm) and similar basophilia (10 210/cmm), with mild normocytic normochromic anemia (Hb 11.6 g/dl). PBS showed left-shifted deviation of leukocytes up to 6% myeloblasts, with 7% basophils and all myeloid maturation forms present. A BM aspirate followed, showing granulocytic lineage hyperplasia and 6% myeloblasts, revealing chronic myeloproliferative neoplasia, chronic phase. Cytogenetics followed, showing presence of Philadelphia chromosome 100%, t(9;22). A BM biopsy was also performed, confirming previous results and molecular biology showed presence of BCR-ABL1 transcript (b2ba2, p210).

However, during a careful clinical examination, besides mild splenomegaly (~2 cm under costal margin), there was a small left parasternal mass, without remarkable clinical elements, approximately 3 cm in diameter, dismissed by the patient as he believed it to be a post-traumatic injury. We decided to go further and perform a biopsy of the lesion, which proved presence of diffuse

proliferation of blast cells, with rare mature cells. Immunohistochemical examination showed CD34 and TdT positive blast cells, positive MPO in frequent myeloid cells, neoplastic proliferation of B cells, positive for PAX 5 and CD10/CALLA, CD3 negative. Thus, we concluded the following diagnosis: extramedullary B lymphoid blast crisis associated with CML.

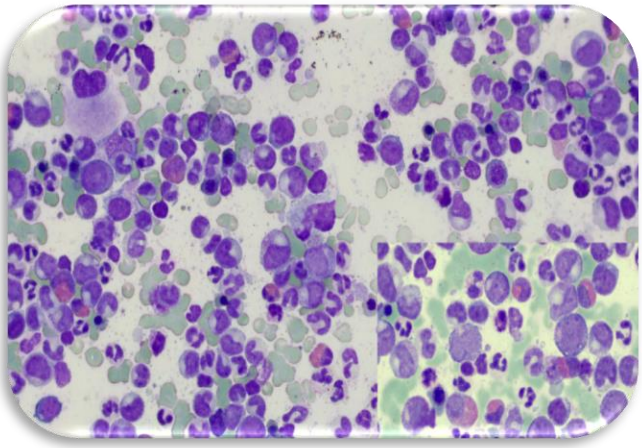

Figure 2. *♂ H.I. Bone marrow aspirate, 40x, Giemsa; chronic myeloid leukemia aspect: left-shifted deviation of granulocytic lineage up to myelocytes, 10:00 dwarf megakaryocyte spotted (small, hypolobulated) - courtesy of Hematology Laboratory of Colțea Clinical Hospital.*

Therapeutic approach consisted of TKI 2nd generation/dasatinib and GRAAPH protocol, compatible with acute lymphoblastic leukemia (ALL) regimens, followed by consolidation with allogeneic hematopoietic stem cell transplant (alloHSCT). HLA typing of patient and 1st degree relatives (brothers) followed, showing no compatibility. Patient eventually refused undergoing alloHSCT. A lumbar puncture was performed, showing no CNS disease and CNS dissemination prophylaxis was applied.

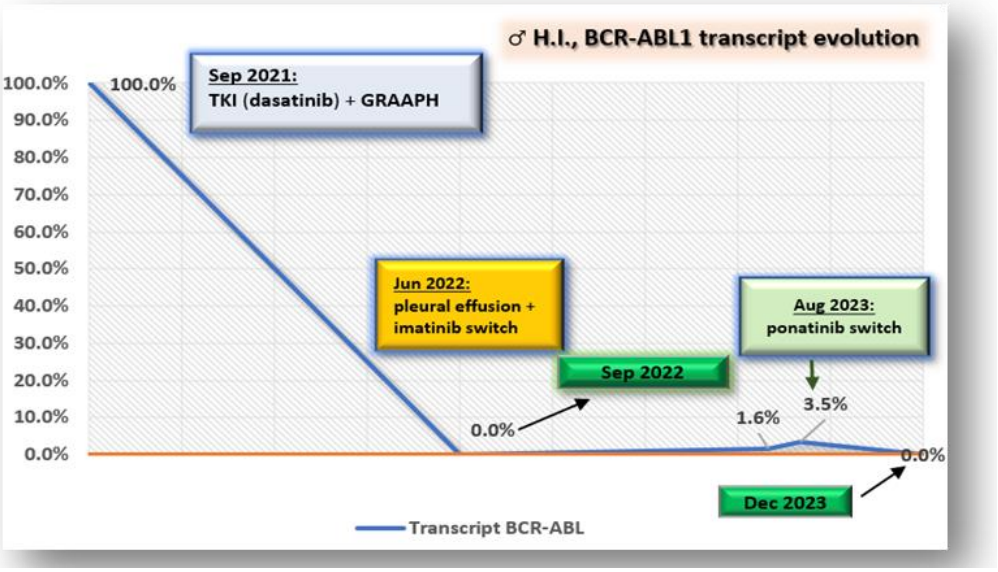

Figure 3. *Therapeutic dynamics during treatment of CML lymphoid BC and BCR-ABL transcript evolution*

Briefly, complete hematological, morphological, molecular and cytogenetic remission was obtained. Dasatinib was continued until June 2022 when the patient developed right pleural effusion; flow cytometry of pleural fluid showed 94% mature lymphocytes. Consequently, we discontinued dasatinib and initial switch was with imatinib. However, the patient presented with molecular relapse in August 2023 and we decided to

go further with ponatinib, a 3rd generation TKI. Of important notice, resistance mutations panel and T315I mutation were performed, with negative result. Current status of the patient is favourable, despite not undergoing alloHSCT, maintaining complete remission with BCR-ABL1 undetectable, without other specific symptoms and good tolerance of ponatinib (minimal adverse event such as a diffuse non-pruritic rash well managed with topical drugs).
Third case shows a 50 y.o. female, Z.M, who presented in February-March 2015 with asthenia, abdominal discomfort and severe hepatosplenomegaly. Laboratory work-up showed similar results as the previous cases, however the PBS revealed presence of numerous megakaryocytes and megakaryoblasts, with 50% myeloid pleomorphic blasts and 18% basophils. BM aspirate morphology showed left-shifted deviation of leukocytes, basophil precursors, undifferentiated blast cells and hypercellular megakaryocytic lineage with frequent megakaryocytic islets, micromegakaryocytes and megakaryoblasts, revealing blast phase of chronic myeloid leukemia, possibly megakaryocytic. Cytogenetics came back unconclusive and flow cytometry (peripheral blood) confirmed the blast phase of chronic myeloid leukemia, with myeloid and megakaryocytic precursors (32% blasts in CD45 negative region: 62% CD34 and CD41 positive, 38% CD34 and CD42b positive). Molecular biology cleared the picture, showed 100% BCR-ABL1 positivity (p210) and JAK2V617F negativity. On abdominal ultrasound spleen size proved to be over 22 cm long axis, in close contact with the liver.
Therapeutic approach consisted of TKI introduction, 1st generation/imatinib (given its availability at that time point), and 3+7 induction regimen with cytarabine and doxorubicin. However, follow-up BM aspirate and flow-cytometry proved disease resistance with 36% megakaryoblasts. Cytogenetics showed 50% positive Philadelphia chromosome and platelet count reached over 1000 x 10^3/mcl. MEC protocol (mitoxantrone, etoposide and cytarabine) followed altogether with dasatinib, with complete hematological, morphological, molecular and cytogenetic remission.
Importantly, even though the patient had a compatible related donor (sister), she refused alloHSCT procedure. She had good tolerance and adherence to dasatinib until May 2023, when pleural effusion ensued. Dasatinib was discontinued and bosutinib was started. Current status of the patient is favourable, maintaining complete remission to this day (almost 10 years from diagnosis), with undetectable BCR-ABL and good clinical state. TKI treatment is well tolerated, without major adverse events.

Discussions

Blast crisis (BC) in CML still represents a major challenge. Even though it resembles de novo acute leukemia, it remains a difficult to treat clinical entity. TKI era brought major improvements to therapy and outcomes. The main goal is to achieve a second chronic phase and to consolidate treatment response with alloHSCT in eligible patients. Despite research advancements in this field, favourable outcomes are rare without undergoing alloHSCT procedure. (1)
Rare instances of CML should not be dismissed, as previously proved by apparently insignificant clinical elements which can drastically change disease course, treatment approach and survival.
BC can be myeloid, lymphoid or mixed lineage, the most frequent being myeloid, followed by lymphoid (up to 1/3 of cases). Lymphoid BC usually presents without undergoing a triphasic evolution, with no accelerated phase and mild splenomegaly, typically of the B-cell lineage. It is similar to Ph+ ALL and it is associated with poor long-term outcome, despite the use of TKIs. (2)
The majority of lymphoid BC are usually medullary, with rare instances of extramedullary lymphoid BC. The lymph nodes are considered to be the most frequent extramedullary presentation. The majority of BC are considered to stem from additional chromosomal anomalies, however lymphoid BC gains fewer additional anomalies compared to myeloid BC. B lymphoid BC is usually associated with loss of the short arm of chromosome 9, which harbours genes with great impact in B-cell differentiation like PAX5 for example. Myeloid BC is twice as common; however, its prognosis is considered to be worse. CML presenting with megakaryocytic BC is extremely rare and up to this day, few cases have been reported worldwide, with poor outcome and extreme resistance to available treatment. (1), (3), (4), (5), (6)
In what concerns TKI choice, dasatinib showed improved outcomes in patients with intermediary/high-risk disease in chronic phase CML, with shorter times to MMR and DMR (deep molecular response) and better long-term and progression-free survival, compared to imatinib. It is a potent 2nd generation TKI, with good CNS penetration (through the blood-brain barrier), with great therapeutic potential in targeting intracranial leukemic disease and CNS relapse, thus representing a feasible option for CNS dissemination prophylaxis even in patients who proved negative for CNS disease at diagnosis in lymphoid BC. However, recent murine studies showed that ponatinib, a 3rd generation TKI, achieved even better CNS penetration compared to 2nd generation TKIs, in comparative pharmacokinetic studies, also having a broader plasma half-life compared to dasatinib. These data supported our decision in choosing a 3rd generation TKI for our second patient, with extramedullary lymphoid BC-CML, when dasatinib was no longer a safe option due to important

pleural effusion development and resistance to imatinib appeared. We also took into consideration the fact that our patient refused undergoing alloHSCT procedure and as such a penury of treatment approaches ensued which required careful consideration of next choice of TKIs- another 2nd generation TKI or going further and switching to 3rd generation TKI. (7), (8), (9), (10), (11), (12), (13)

Bosutinib, another 2nd generation TKI, was mostly used for chronic phase CML and regarding BC- predominantly myeloid ones. In what concerns lymphoid BC, there is a scarcity of data concerning bosutinib and the available case reports and recent studies have showed its usage next to other immunotherapies (inotuzumab-ozogamicin, antibody-drug conjugate targeting CD22 expressed on immature B lymphocytes) and fewer reports next to classical combined chemotherapy. These data prompted our therapeutic approach switch for our third patient, given the fact that she has long-term complete remission with dasatinib, no relapse during follow-up and a myeloid subtype BC. (14), (15), (16)

In conclusion, important advancements in the treatment of CML have been made, however there is plenty of space regarding improvement of CML in BC management, especially concerning rare presentations. Durability of a certain treatment option/line is not guaranteed, given the molecular heterogenous pattern and the degree of genomic instability associated with BC CML; alloHSCT still remains an option for some patients and it should be more accurately integrated in the treatment plan altogether with strict monitoring schedules of markers associated with CML progression. (17)

Abbreviation list

ALL- acute lymphoblastic leukemia
alloHSCT- allogeneic hematopoietic stem cell transplant
BC- blast crisis
BM- bone marrow
CML- chronic myeloid leukemia
CNS- central nervous system
DMR- deep molecular response
EUTOS/ELTS- EUTOS long-term survival score
MMR- major molecular response
PBS- peripheral blood smear
TKI- tyrosine kinase inhibitor

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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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