Review Article

NPM1 Mutated, BCR-ABL1 Positive Myeloid Neoplasms: Review of the Literature

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Abstract. Breakpoint cluster region - Abelson (BCR-ABL1) chimeric protein and mutated Nucleophosmin (NPM1) are often present in hematological cancers, but they rarely coexist in the same disease. Both anomalies are considered founder mutations that inhibit differentiation and apoptosis, but BCR-ABL1 could act as a secondary mutation conferring a proliferative advantage to a pre-neoplastic clone. The 2016 World Health Organization (WHO) classification lists the provisional acute myeloid leukemia (AML) with BCR-ABL1, which must be diagnosed differentially from the rare blast phase (BP) onset of chronic myeloid leukemia (CML), mainly because of the different therapeutic approach in the use of tyrosine kinase inhibitors (TKI). Here we review the BCR/ABL1 plus NPMc+ published cases since 1975 and describe a case from our institution in order to discuss the clinical and molecular features of this rare combination, and report the latest acquisition about an occurrence that could pertain either to the rare AML BCR-ABL1 positive or the even rarer CML-BP with mutated NPM1 at the onset. Differential diagnosis is based on careful analysis of genotypic and phenotypic features and anamnestic, clinical evolution, and background data. Therapeutic decisions must consider the broader clinical aspects, the comparatively mild effects of TKI therapy versus the great benefit that might bring to most of the patients, as may be incidentally demonstrated by our case history.

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Introduction. Mutations in the *NPM1* gene are the most frequent genetic abnormalities in acute myeloid leukemia (AML) and are highly specific for de novo AML.[1] The Breakpoint cluster region - Abelson (*BCR-ABL*) fusion gene is the genetic hallmark of chronic myeloid leukemia (CML) but can also be found in approximately 30% of acute lymphoblastic leukemia (ALL) and rarely in AML (0.3–3% of newly diagnosed cases).[2–4] In the updated World Health Organization (WHO) classification published in 2016, AML with BCR-ABL has been introduced as a provisional new entity.[5,6] To the best of our knowledge, the co-occurrence of the *BCR-ABL* fusion gene and *NPM1* mutations in de novo AML has been reported in only a few cases. In this review, we analyzed all the BCR/ABL1 plus NPMc+ published cases since 1975 and a case from our institution to present common clinical and molecular features of this rare disease.

t(9;22)(q34.1;q11.2) BCR-ABL. Among human cancers, AMLs are relatively genetically simple and stable diseases featuring the fewest mutations variety and average. AML genomes contain a median of 13 coding mutations (single nucleotide variants and insertion/deletions) and an average of less than one gene-fusion event.[7,8] Most of the fusions derive from translocation events, and Philadelphia chromosome t(9;22)(q34.1;q11.2), generating the BCR-ABL1 chimeric protein, was the first genetic aberration associated with human cancer: Chronic myeloid leukemia (CML). BCR-ABL activates proliferation signaling pathways (RAS and STAT5, STAT1 and STAT6 signaling, PI3-K and AKT/PKB pathways), analogously to PML/RARa in APL inhibits PTEN,[9,10] interferes with the focal adhesion complex (PAXILLIN, FAK), induces abnormal integrin signaling (FAK/CRK-L/SDF-1) and has anti-apoptotic activity (PI63K/Akt/STAT5). In addition, BCR-ABL has been shown to generate a "mutator" phenotype downregulating homeostatic controls and DNA repair pathways and promoting the expression of DNA-polymerase-beta, which is prone to copy errors during DNA replication.[11] Since no CML-BP with lymphoid phenotype carrying the NPM1c+ mutation was ever reported, we will not address the subject of Ph1+ALL. Contrarily to what could be expected only a few years ago, myeloid neoplasms carrying the *BCR-ABL* transcripts are a composite subset of hematological disorders. If the principal disease, CML, in which BCR-ABL1 is involved, has well-characterized features and standardized diagnosis and therapy, the picture is composite for the other neoplastic diseases. 2016 WHO classification of myeloid neoplasms and acute leukemia distinguish, other than CML, two more entities: one mixed phenotype acute leukemia (MPAL) with BCR-ABL1, and the provisional AML with BCR-ABL1.[6] Since no CML-BP with lymphoid phenotype carrying

the NPM1c+ mutation was ever reported, we will not address the subject of Ph1+ALL.

Nucleophosmin. Nucleophosmin (NPM1) is present in high quantities in the granular region of nucleoli but shuttles between nucleus and cytoplasm, acting as a chaperone. Chaperones are molecules that associate with target proteins, organize their structure, convoy them to the appropriate place, and molecular aggregate but are not part and have no function in that aggregate.[12,13] *NPM1* has been identified as the most frequently mutated gene in AML patients, accounting for about 30% of cases,[14–16] the vast majority of which with normal karyotype. At onset, NPM1 mutation associates with a less severe prognosis, but clonal evolution can lead to additional genetic abnormalities and worst prognosis.[1,16,17] NPM1 gene mutations in AML lead to a new C-terminus sequence in the mutant protein, that, as compared to the wild-type protein, lacks the nucleolar binding site and acquires a nuclear export signal: mutated NPM1 is confined to cytoplasm, its absence from the nucleus seems to be the basis for the oncogenic phenotype since the protein plays a role in chromatin remodeling, centrosome duplication, DNA replication, recombination, transcription, and repair as well as in the control of cell cycle progression and survival in response to a variety of stress stimuli.[12,18–21]

The Paradigm of Leukemogenesis. Mutations within a cell can influence the rate of acquisition of other lesions. After the initiating mutation, there might be a gradual accumulation of additional genetic alterations or accelerated progression due to genomic instability or catastrophic genetic events, including chromothripsis.[22–27] The number of identifiable driver mutations differs between AML cases. Although most cases harbor three or more identifiable drivers at the time of clinical presentation, human sequencing data describe many AML with only one or two identifiable driver mutations.[24,28] According to the model of Gilliland and Griffin, the paradigm of leukemogenesis features a class II mutation as leukemia-initiating event, causing inhibition of differentiation and apoptosis, cooperating with a class I mutations conferring a proliferative advantage to the clone.[29,30] In 2013 the Cancer Genome Atlas Research Network classified three sets of genes with the strongest patterns of mutual exclusivity. For the purpose, they used whole genome or whole exome sequencing and statistical analysis of 200 de novo AML cases selected from a set of more than 400 samples to reflect a real-world distribution of subtypes. The first set comprised the transcription-factor fusion genes and mutations involving *NPM1*, *RUNX1*, *TP53* and *CEBPA*, the second set the mutations in genes encoding *FLT3* or other tyrosine kinases (TK), serine-threonine kinases, protein tyrosine phosphatases, RAS family proteins, and the third set included mutations in *ASXL1* and genes

encoding components of the cohesin complex, other myeloid transcription factors, and other epigenetic modifiers.[7] The association of *BCR-ABL1* and mutated *NPM1* in the same clone is unusual but not contradictory to either of the models if *NPM1* is the founder, class II mutation, and *BCR-ABL1* acts a class I mutation, conferring a proliferative advantage to the affected cells. BCR-ABL1, even though capable of transforming hemopoietic stem cells single-handed and causing per se CML and diverse acute leukemias (Ph1+ ALL, MPAL and AML), could be working as a class I mutation[31] since the molecular aberration was found in tumor subclones and even in oligoclones in otherwise normal bone marrow.[32,33] However, would that be possible to reverse the rank of the mutations, as in a CML blastic phase (CML-BP) clone carrying mutated NPM1 evolving from an NPM1-negative chronic phase disease? Moreover, how to discriminate between de novo Philadelphia positive AML and a CML diagnosed at BP onset? Even though identical regarding two substantial features of the genetic profile, the two conditions must have different biology. The presence of BCR-ABL1 protein ab initio, thus in tumor-initiating cells and all the disease clones, must confer the phenotype, natural history, and clinic of CML. Conversely, the emergence of a BCR-ABL positive clone as a type I mutation in an NPM1 mutation expressing clone is not more than a concomitant feature in the characteristic of acute leukemia, in a way not entirely different from a FLT3 activating mutation (**Figure 1**).

NPM1 Mutated and BCR-ABL1 Positive Myeloid Neoplasm. To the best of our knowledge, only a few cases of de novo AML with *BCR-ABL1* and *NPM1* mutations were published in the last decades (**Table 1**). Bacher *et al*. describe a case with normal karyotype AML (FAB M4) and an *NPM1* mutation, the occurrence of a Philadelphia positive subclone in an *NPM1* mutated AML patient emerging at relapse of the disease. This patient received initially high dose of chemotherapy, and also intensive chemotherapy with high dose cytarabine and mitoxantrone after relapse, unfortunately dying from progression 26 months from diagnosis.[31] Single cases with Philadelphia positive subclones in *NPM1* mutated AML had previously been reported by Suzuki *et al*.[34] and Verhaak *et al*.[35] Palmisano *et al*. reported a patient who maintained the *NPM1* mutation at relapse of the disease, whereas the t(9;22) was lost.[36] Konoplev *et al.* analyzed NPM1 and ABL1 genes, often mutated in AML and CML-BP patients, respectively, to gather insights into the relationship between Ph+ AML and CML-BP. They studied 9 Ph+ AML and 5 CML-BP patients at the onset. Two out of 9 Ph+ AML patients had *NPM1* mutations and were alive 36 and 71 months after diagnosis. All Ph+ AML had no mutation in the *ABL1* sequence, no *NPM1* mutations were identified in

the CML-BP group, and one CML-BP patient had *ABL1* mutation. The Authors argue that Ph+ AML is distinct from CML-BP.[36] Reboursiere *et al.* describe one case harboring a BCR-ABL p210 transcript level of approximately 10% with *NPM1* gene mutation. The patient received induction therapy with mitoxantrone, daunorubicin, and cytosine arabinoside and two courses of high-dose cytosine arabinoside consolidation therapy followed by allogenic hematopoietic stem cell transplantation (allo-HSCT). Eleven years after allo-HSCT, the patient remained in continuous complete molecular remission.[37] Mattioti et al. report a patient diagnosed with AML harboring a complex three-way translocation t(9;22;12)(q34;q13;q11) encoding for two isoforms of *BCR-ABL* transcript (b3a2;b2a2) and a concomitant type A mutation in the *NPM1* gene. The patient was started on initial cytoreductive treatment with hydroxyurea for ten days and was subsequently treated with second-generation tyrosine kinase inhibitor (TKI) dasatinib due to the central nervous system's high risk involvement and extramedullary localization. Unfortunately, the patient died after 3 months of treatment.[38] Studies regarding CML have shown that in some cases transcript, b2a2 has slower molecular and inferior response rates to TKI and a poorer long-term outcome,[39] but at present, no reliable data are available regarding the prognostic value of the different transcripts in AML. Neuendorff *et al.*, in an exhaustive review, describe 6 *NPM1* mutated at primary diagnosis out of 126 cases of de novo *BCR-ABL1+* AML. At least 3 of these 6 *NPM1 BCR-ABL1+* AML patients were long-term survivors, which notwithstanding the exiguity of cases, is a large percentage.[40]

From the clinical point of view, sometimes the presence of the *BCR-ABL1* hybrid transcript could not clarify the adjudication since a precise distinction between AML and CML-BP at onset is still to be defined, which poses problems of diagnosis and therapy, most of all about the timing and efficacy of TKI therapy. Notwithstanding the rarity of cases, it seems clear that AML with *BCR-ABL1*, in general, does not always respond well to TKI therapy;[40] conversely, a TKI naïve CML must benefit from TKI therapy.[41]

Experience in Our Institution. Here we want to narrate the case of a patient, 43 years of age, male, diagnosed in April 2013 at a different country institution supposedly with a CML onset in BP and treated with 3 days Idarubicin plus seven days of high dose Aracytin (IA 3+7) resulting in complete hematological remission on day 26. The patient had experienced a series of severe complications during the induction therapy. The routine molecular assessment had documented positivity for BCR-ABL1 (p210-B3A2) translocation and *NPM1* mutation A.[42,43] The patient, with residual hepatic toxicity, was prescribed Dasatinib 100mgr as maintenance therapy. The diagnosis was well
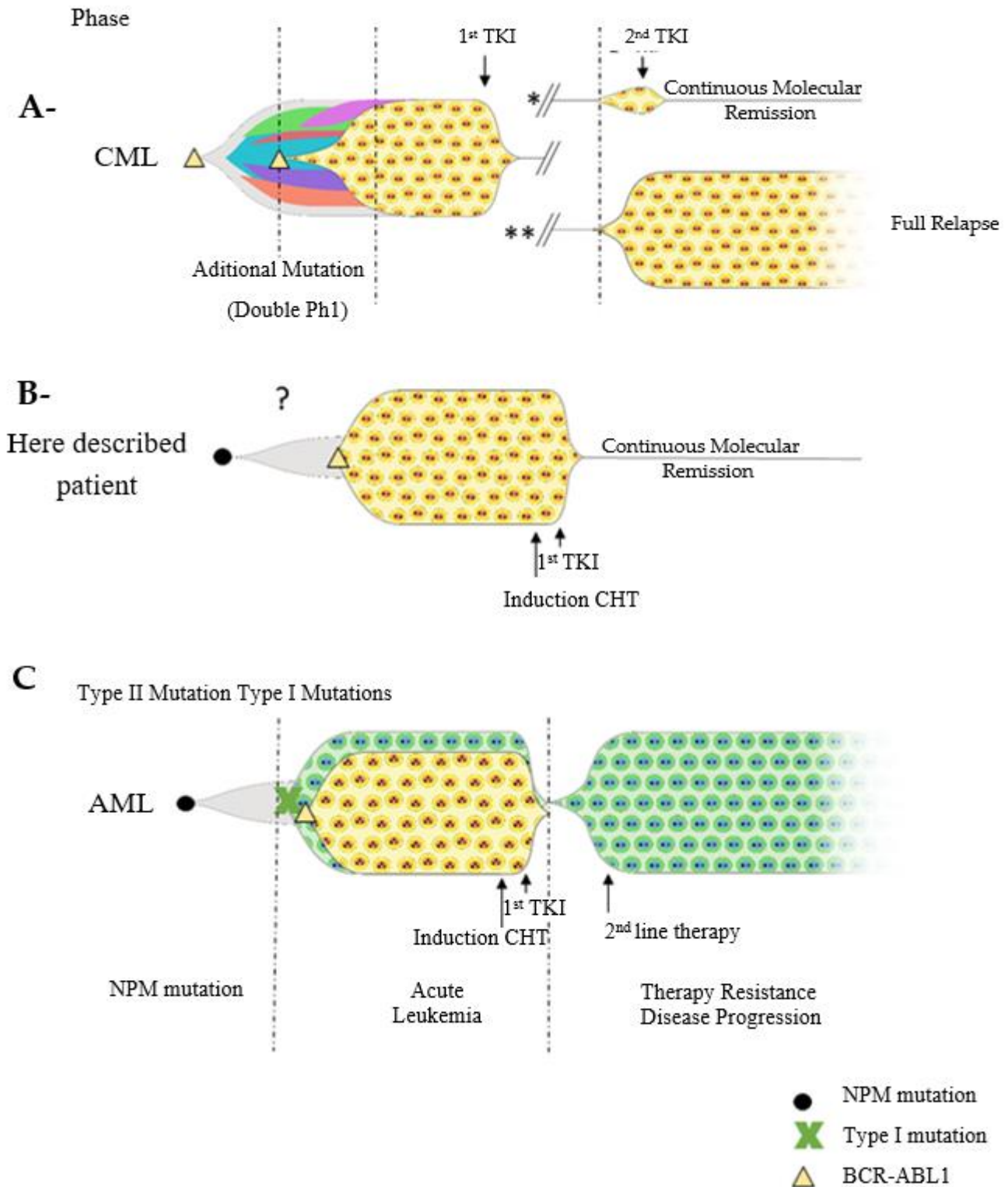
Figure 1. Clonal evolution patterns for AML and CML.
A- BCR-ABL1 causes a "mutator" phenotype downregulating homeostatic controls and DNA repair pathways. Several subclones develop until additional mutations (double Ph1, +8, +19, +21, i(17q), abnormalities of chromosome 7, mutation of TP53, RB1, MYC, CDKN2A, RAS, RUNX1, and EVI1 genes) generate the blastic phase clone. The disease is often chemoresistant, and TKI therapy does not always work, but is still the best therapeutic option, particularly in TKI naïve patients. After remission, the disease could be controlled for a lasting remission; emerging resistant clones can be controlled with a second TKI (*) or develop into a full relapse of the BP(**). B- The patient, here described, responded to induction therapy and maintained continuous remission under TKI therapy. C- Major clonal evolution patterns during AML insurgence and relapse implicate that the disease's founding clone gains mutations and evolves into the disease. After remission, a relapse clone(s) could arise from the original under the selective pressure of therapy. Otherwise, a subclone of the initial clone survives therapy, gains additional mutations, and expands at relapse. In both models, a founding type II mutation is followed by cooperating type I mutations able to convey a proliferative advantage. Often in BRC-ABL1+ AML patients, the relapsing clone lacks BCR-ABL1 mutation and therefore is insensitive to TKI therapy.

Table 1. AML with BCR-ABL1 and NPM1 mutations.

Case Reported	Genetics	Therapy	Outcome	Ref
AML (FAB M4)	Diagnosis: NK, NPM mut Relapse: NPM mut; t(9;22)	High dose chemotherapy. Relapse: High dose chemotherapy, high dose cytarabine, high mitoxantrone	Died from progression (26 months)	31
AML (1 of a total of 190 cases analyzed)	NPM mut; t(9;22)	Japan Adult Leukemia Study Group (JALSG) protocols	Poor prognosis	34
AML (1 of a total of 275 cases analyzed)	NPM mut; t(9;22)	Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) protocols	Poor prognosis	35
Two out of 9 Ph1+ in 2241 AMLs (0.5%). (FAB: Patient1 M1; Patient2 M2)	NPM mut; t(9;22)	Not reported	Alive 36 and 71 months after diagnosis	36
AML	NPM mut; t(9;22) (P210)	Induction: Mit, Dau, and CA. Consolidation: two courses of high-dose CA followed by allo-HSCT	Alive 11 years after allo-HSCT	37
AML	NPM mut, t(9;22;12) (q34;q13;q11) (b3a2;b2a2)	Hdu ten days + Das	Died after 3 months of treatment	38
Six out of 126 AML Ph1+	NPM mut, t(9;22)	Not reported	3 long-term survivors, 3 no available data	40
Here described patient	NPM mut-A, BCR-ABL1 (b3a2)	Induction: IA 3+7 Maintenance: Das	Alive in continuos CR for 7 years	-

Mit: mitoxantrone, Dau: Daunorubicin, CA: cytosine arabinoside, Mut: Mutation allo-HSCT: allogeneic hematopoietic stem cell transplantation, Hdu: Hydroxyurea, Das: Dasatinib, CR: complete remission, NK: Normal karyotype3 days, IA 3+7: Idarubicin plus seven days of high dose Aracytin.

documented as for the extension of the search for the mutations but essential since we were not detailed about the FAB and immunophenotype of the blasts, quantities of the mutated transcripts, or about any other clinical aspect that would explain the choice of CML-BP over AML with *BCR-ABL1+*. In our opinion is of interest that the case was labeled as CML-BP, yet the clinical perspective and indication were that of a de novo AML with *BCR-ABL1*: intensive induction chemotherapy with additional TKI maintenance therapy, then consolidation and allo-SCT.

On day 45, our bone marrow evaluation showed hematologic morphologic remission, molecular remission of the *BCR-ABL1* transcript (p210 transcript was 0.069% with MR3 sensitivity, p190 was 0,0% negative MR3 sensitivity) and molecular remission of the *NPM1* mutated transcript (0.025 of *NPM1* mutation A copies every 104 copies of *ABL*, cut off value 0.03).[44] Of note that only a small percentage, less than 10%, of CML-BP patients, achieves molecular remission after frontline chemotherapy plus TKI therapy.[41] In contrast, almost one in three of AML NPM1 mutated patients achieve molecular remission 30 days after frontline therapy.[45] The search for a compatible donor among siblings was unsuccessful, we consulted with the patient. We agreed to postpone intensive chemotherapy mainly for the high risk of a recurrence of the intestinal bleeding, at the same time the patient did not agree to start a search for an unrelated compatible donor. One year since onset p210 transcript was undetectable with MR5 sensitivity, we stop essaying p190, and the *NPM1* mutated transcript remained in molecular remission (0.03 of *NPM1* mutation A copies every 104 copies of *ABL*, cut off

value 0.03). After more than 6 years, the patient is still in continuous profound molecular remission of the BCR-ABL1 (undetectable transcript with MR5 sensitivity) and remission of the NPM1 transcripts. Still assuming Dasatinib, the dose was interrupted for 30 days and then reduced by half to 50 mg per day due to a chemical pleuritis about 12 months ago. The interruption and lowered dose did not cause any variation in the molecular remission of both transcripts. Since all disease-free survival (DFS) curves tend to plateau after 2-3 years of follow-up and relapse after 5 years of DFS are rare events, we may say the patient was fortunate not to undergo intensive chemotherapy and allo-SCT.

Nevertheless, is this patient eligible for ending TKI therapy? It all depends on the diagnosis. A CML-BP in remission is not eligible in any case for stopping TKI therapy. Conversely, an AML in continuous molecular remission after 6 years could be considered for ending the treatment.

Differential Diagnosis. CML primary blast phase is an infrequent event, and the secondary blast phase is usually marked out by patients' medical history. In the lack of a previous CML diagnosis, most BP cases must carry the clinical and morphologic stigmata of the chronic phase. Thus anamnestic and clinical features, histology and morphology, immunophenotype, and genetic can be of help. The presence of basophilia often accompanies blast cell expansion and disease acceleration in CML, whereas it is not a common feature in de novo AML, the same for splenomegaly. In BP, bone marrow megakaryocytic count is increased in most cases with perisinusoidal distribution and no

clusters, hypolobation of nuclei, and the presence of micromegakaryocytes. Broadly 75% of BP show a myeloid phenotype and in more than 80% of cases feature additional genetic abnormalities (double Ph1, +8, +19, +21, i(17q), abnormalities of chromosome 7, mutation of *TP53*, *RB1*, *MYC*, *CDKN2A*, *RAS*, *RUNX1,* and *EVI1* genes).[46] Of note, ABL1 TK domain mutations are typical of CML-BP and are not restricted to patients with prior TKI exposure. In a study of unselected TKI-naïve CML-BP patients, 5 of 19 patients had *ABL1* mutations.[45] *ABL1* mutations have not been reported in Ph+ AML patients.[15] Under the genotypic profile, there is a link between *BCR-ABL1* rearrangement and some features associated with the lymphoid phenotype. Nacheva et al. studying 9 de novo AML Ph1+, 6 myeloid, and three biphenotypic leukemia showed that BCR-ABL1+AML blasts often are burdened by aberration commonly associated with lymphoid lineage tumors (deletions of *IKZF* and *CDKN2A/B* and concomitant loss within the immunoglobulin and T cell receptor gene complexes) that are all also found in *BCR-ABL1*+ ALL and CML chronic phase, but not in myeloid CML-BP.[47]

The presence of lymphoid markers, not sufficient for a classification as MPAL according to WHO, is in line with a finding by Atfy *et al*., who found in all nine cases of de novo Ph1+ AML: CD33 and CD13 markers, and CD64 in 8 of them. MPO was positive in 9/9 patients by flow cytometry. The B-lymphoid marker CD79a was positive in one, T-lymphoid marker CD7 in 4, CD24 in one case, and CD19 was found in two AML cases that could be considered as FAB M2. Seven of the nine AML patients had an aberrant expression of lymphoid markers. Stem cell markers CD34 were positive in 6/9, and TDT was positive in 1/9 cases. According to the FAB, one case was diagnosed as M0, 3 cases as M1, 4 cases as M2, and one case as M4.[48]

In a recent study among 46 cases of myeloid BP, 76% expressed CD34, and 74% expressed CD117. Myeloperoxidase expression was noted in a variable proportion of precursor cells in 85% of cases. TDT was expressed in 37% cases, 14 cases expressed markers outside of the standard myeloid phenotype, and two expressed markers of more than one lineage (B or/and T).[49]

In a retrospective study of 477 BP cases in 20 years encompassing the introduction of TKI therapy, Jain P et al. found that, for 77 patients diagnosed as BP at the onset, first-line treatment included TKI alone (24 patients; 34%), TKI plus chemotherapy (41 patients; 58%), non-TKI-based therapies (2 patients; 3%). Clonal evolution under therapy pressure must play a role since patients with de novo BP had a longer overall survival time (OS) compared with patients who transformed from CML-Chronic Phase/CML-Acute Phase (P<.0001). The most effective treatment option

was the combination of a TKI with chemotherapy. Patients who achieved morphologic hematologic remission (MHR) or complete cytogenetic remission (CCyR) or major molecular response (MMR) after initial BP treatment had a significantly longer failure-free survival (FFS) (P<.0001) and the achievement of MHR and/or CCyR emerged as the most significant independent predictors of survival.[41] In a 2019 review, Soverini et al. state that 2 to 5% of CML patients present in accelerated phase (AP) and 2 to 7% in BP and that, as a whole, AP/BP patients display a high degree of genetic instability, with an accumulation of additional genetic and cytogenetic abnormalities that reduce sensitivity to TKI. However, the paper does not address the genetics of de novo AP/BP patients.[50]

In a study published in 2015, Klco et al. confirm that among 71 patients with de novo AML, 18 patients carrying *NPM1* mutated alleles were cleared below the threshold of 2,5% (5% of cells) at day 30 from induction therapy start, and those patients have the best chances to have a long first remission. Seemingly type I mutations as *FLT3*, *KRAS*, or *NRAS* were usually cleared on day 30, suggesting that subclones containing these mutations may be highly sensitive to induction chemotherapy, but of course, those patients tend to relapse early and have a poor prognosis.[51]

Thus would not be unusual that in our case, if considered as an AML, the molecular profile was nearly negative for both mutations on day 45. Conversely, a CML-BP in hematological remission after just one intensive chemotherapy cycle and after no more than 18 days of TKI therapy should register at least a substantial regrowth of clonal *BCR-ABL1* positive hematopoiesis. As exposed before, there are several suggestions but not certainty about discriminating de novo Ph1+AML and CML-BP at the onset. In the absence of a previous CML history, differential diagnosis is based on the global analysis of histologic, immunophenotype, and genetic features, which in most cases singularly are not decisive in differentiating the two conditions, but taken all together may lead to a possible assignation. We summarize the differential characteristics in **Table 2**. It is interesting as some statistical modeling reports implicate the role of functional NPM1 in conveying tumorigenic signals from the BCR-ABL1 oncoprotein to ribosome biogenesis, affecting cellular growth.[52,53] Thus, in theory, *NPM1* mutation could hamper, in part, BCR-ABL1 oncogenic phenotype, which explains the rarity of the finding and renders NPM1 a highly improbable candidate for BP transition.

Conclusions. In conclusion, there seems to be only one clear precedent of CML-BP carrying the NPM1 mutation, convincing under the clinical point of view since we are given no information about the mutational

Table 2. Differential characteristics between CML-BP and AML.

Diagnosis	AML	CML-BP	Ref
CML hematopoiesis islands	0	10	45
ABL1 TK domain mutation in *BCR-ABL1*	0	10	36,46
IKZF, *CDKN2A/B*, Ig, *TCR* deletions	0	10	47
Basophilia >2%	1	9	45,54,55
Double Ph1, BCR-ABL1 hyper expression	1	9	45,56
Splenomegaly	2	8	40,45,55
Bone marrow cellularity > 90%	2	8	45,55
Mean myeloid/erythroid ratio > 3	2	8	42,45,55
Co expression of lymphoid markers	2	8	48,57
Chemoresistance to anthracyclines and cytarabine	3	7	22,32
+8, +19, +21, i(17q), abnormalities of chromosome 7			
TP53, *RB1*, *MYC*, *CDKN2A*, *RAS*, *RUNX1*, *EVI1* mutations	4	6	1,45,58,59
TKI resistance	7	3	41,51
FLT3 mutations	9	1	1,7,60
NPM1	9	1	5,52,53
CBF mutation+ p190 transcript	9	1	61,62
Normal hematopoiesis islands	10	0	45
Karyotype with < 100% Ph1 positive metaphases	10	0	45,63

Schematic representation of diagnosis probabilities according to clinical features: 10 indicating maximum and 0 minimum of probability.

status of the CP,[64] whereas double mutated NPM1 BCR-ABL1+ AML, although rare, has been clearly devised as part of the AML with mutated NPM1 classification. We feel that NPM1 mutation presence has to be considered decidedly as a sign of AML rather than BP. Therapeutic decisions must consider the broader clinical aspects, the comparatively mild side-effects of TKI therapy versus the great benefit that might bring to most of the patients, as our case history may incidentally demonstrate it. Even considering all the premises, and even after the chemical pleuritis he suffered after five years of Dasatinib at 100 mg per day, a complication promptly resolved with 30 days interruption, diuretic, and corticoid therapy. However, we are not counseling to end TKI therapy; since there are no antecedents to guide us, we rather play safe continuing a course of action that was highly effective and with affordable side effects so far.

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