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Rare AML Presentation with NPM1 Mutated, BCR-ABL1 Positive Myeloid Neoplasms with additional DNMT3A mutation and RUNX1/PRDM16 Fusion: Review of the Literature

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Abstract

(BCR-ABL1) Breakpoint cluster region - Abelson chimeric protein and mutated Nucleophosmin (NPM1) are known mutations in hematological cancers, but they rarely are seen in the same disease in a patient. As both of these anomalies are known as founder mutations that are involved in inhibiting 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 which has been adopted worldwide 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 in last decades 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 it could be even rarer CML-BP with mutated NPM1 at the onset. Differential diagnosis is based on careful analysis of genotypic and phenotypic features and clinical history and evolution, and background data. Therapeutic decisions must consider the broader clinical aspects, and should be wisely tailored for, the comparatively mild effects of TKI therapy versus the great benefit that might

bring to most of the patients, as shown in our case history.

Introduction

Mutations in the NPM1 gene are the most frequent genetic abnormalities in acute myeloid leukemia (AML) along with ITD and flt3 and are highly specific for de novo AML.[1] The Breakpoint cluster region - Abelson (BCRABL) 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)BCR-ABL1 observed during the course of hematopoietic malignancies is rare and is associated with poor prognosis.[2–3.] In the updated World Health Organization (WHO) classification published in 2016, AML with BCR-ABL has been introduced as a provisional new entity.[4,5.] 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 wordwide while this additional mutation inDNMT3A mutation and RUNX1/PRDM16 Fusion is never reported before. 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.

Nucleophosmin

Nucleophosmin (NPM1) is present in high quantities in nucleoli as granular regions and is seen shutteling between nucleus and cytoplasm, and act as a chaperone there .Chaperones are molecular structures that work with target proteins, help in organizing structure, convey then to appropriate place, and molecular aggregate but don't become part of that aggregate and have no function in that aggregate [6,7]. NPM1 has been identified as the most commonly mutated gene in AML patients, accounting for about 30% of cases,[8-10] the vast majority of which with normal karyotype. At onset, NPM1 mutation associates with a less favourableprognosis as per AML risk stratification, but clonal evolution can lead to adoption of additional genetic abnormalities and worst prognosis.[1,11,12.] 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.[6,14,15]t(9;22)(q34.1;q11.2) BCR-ABL

AMLs are relatively genetically simple and stable diseases featuring the fewest mutations variety and average among human hematological malignancies. Median of 13 coding mutations (single nucleotide variants and insertion/deletions) are found in Amlgenome and an average of less than one gene-fusion event.[16,17.] Translocation events leads to most of fusion formations , and Philadelphia chromosome t(9;22)(q34.1;q11.2), generating the BCR-ABL1 chimeric protein, was the first genetic aberration associated with hematological human cancer: BCR-ABL in Chronic myeloid leukemia(CML) 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,[18,19] 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). Further, BCR-ABL has been shown to generate a "mutator" phenotype which

down regulating homeostatic controls and DNA repair pathways and has been shown to promote the expression of DNA-polymerase- beta, which is known to be prone to copy errors during DNA replication.[20] Since in our literature search no CML-BP with lymphoid phenotype and carrying the NPM1c+ mutation was ever reported found anywhere , we are avoiding to 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.[21.] Since no CML-BP with lymphoid phenotype carrying the NPM1c+ mutation was ever reported, we avoid addressing the subject of Ph1+ALL.

DNMT3A: Somatic mutations of DNMT3A occur in about 20% of acute myeloid leukemia (AML) patients. They mostly consist in heterozygous missense mutations targeting a hotspot site at R882 codon, which exhibit a dominant negative effect and are associated with high myeloblast count, advanced age, and poor prognosis. DNMT3A is one of several epigenetic modifiers identified as recurrently mutated in acute myeloid leukemia (AML). DNMT3A mutations are associated with cytogenetically normal AML. In vitro experiments indicate that the R882H mutation acts in a dominant negative manner to disrupt the de novo methyl transferase activity of wild type homotetramers. AML patient bone marrow harboring R882 mutations were similarly demonstrated to be hypomethylated compared to patients with wild type DNMT3A. These studies also indicated that non-R882 DNMT3A mutations may act in a functionally distinct manner from R882 mutations. Alternative mechanisms indicate independent prognostic outcomes and treatment protocols may need to be considered for these two classes of DNMT3A mutations.

RUNX1-PRDM16: The t(1;21)(p36;q22) is a recurrent chromosome abnormality associated with therapy-related acute myeloid leukemia (AML). The t(1;21)(p36;q22) is a rare but recurrent translocation. *Refer attached research article

The Paradigm of Leukemogenesis

In process of leukmogenesis, inside cells, other lesion acquisition and formation may result due to mutations. After the initiating mutation, there might be a gradual additional genetic alterations and accumulation of these which lead to accelerated progression due to genomic instability or catastrophic genetic events, includingcomplex chromosomal rearrangement.[22–27] Identifiable driver mutations differs between AML cases in number. 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.[16] 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 .

NPM1 Mutated and BCR-ABL1 Positive Myeloid Neoplasm

Only a few cases of de novo AML with BCR-ABL1and NPM1 mutations were published in the last decades

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;	NPM mut; t(9;22)	Not reported	Alive 36 and 71 months after diagnosis	36

Case Reported	Genetics	Therapy	Outcome	Ref
Patient2 M2)				
AML	NPM mut; t(9;22) (P210)	Induction: Mit, Dau, and CA. Consolidation: two courses of highdose 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.

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]

Experience in Our Institution

We would like to discuss a case of 51 year old male patient who presented with a history of hypertension and gross pallor presented in hospital on 02/08/22 hospital complaining of Realingsensation, fatigue and severe asthenia. There was no previous history of hematological disorders. Blood cell count disclosed Hb 3.3 gm/dL (12.0–16.0 g/dL), Plts 1.17×10^9/L (150–450×10^9/L), a WBC of 96×10^9 (4.30–10.80×10^9/L), basophils <0% (0–1.5%), and with P/S showing left shift and occasional atypical and blasts cells and thrombocytopenia . Bone marrow aspirate showed infiltration by 40% of hypergranular leukemic blasts with few cytoplasmic Auer rods are seen (Figure A and B).

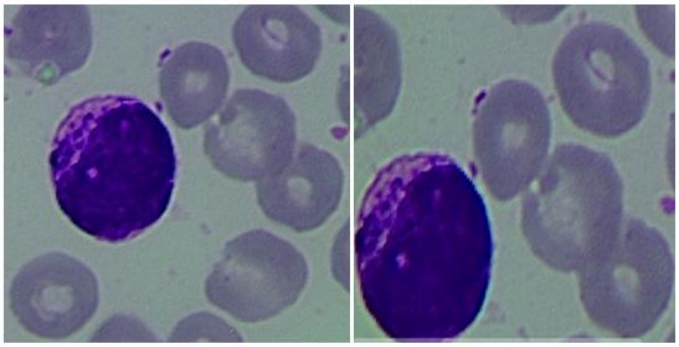

Figure A Figure B

Figure 1: A, B

Immunophenotyping of the leukemic population showed positivity for CD13, CD33, CD117, and MPO and negativity for CD34, HLA-DR, CD38, CD19, CD10, CD20, SURFACE CD22, CD2 cytoplasmic CD3, CD5, CD7, CD56, CD14, CD15,CD36 and CD64, compatible with a diagnosis of AML. Clinical examination showed mild hepatomegaly Cytogenetics FISH report showed Negative for del5q,del7q,del20q, trisomy 8, monosomy 5 and monosomy 7.

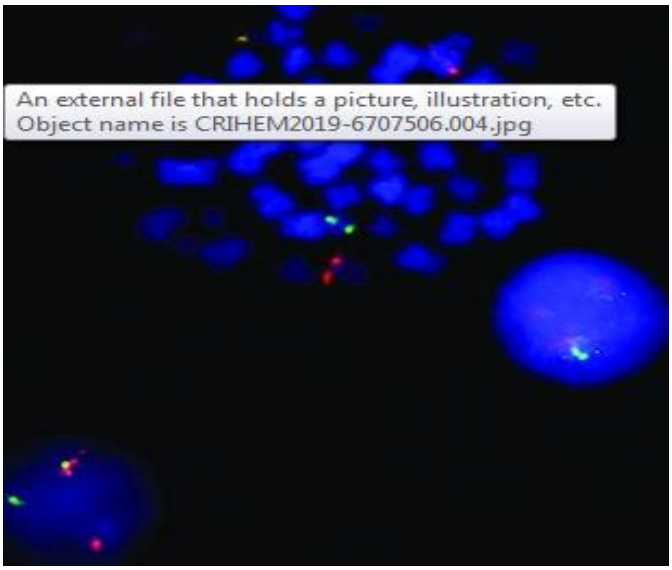

Figure 2: FISH BCR/ABL dual color dual fusion probe.

Next Generation Sequencing showed :NPM1 amino aciod change /exon no. P.W288Cfs*12/12, over all depth /mutantallele percentage 347x/49.3%, oncogene/gain of

function seen .DNMT3A amino acid change /Exon No. p.Arg882Cys/23,overall depth/Mutant Allele Percentage 251x/31.79%, oncogene /loss of function .Presence of translocation between locus chr22:23631808 and chr9:133729451, gene exons BCR(13)-ABL1(2),Read Counts 31185,oncomine Variant Class Fusion .Oncomine Gene Class Oncogene/Gain –of-function, Variant ID BCR-ABL1.B13A2. Other translocation between Locus chr21:36231771-chr1:3102689, Gene (exons) RUNX1(3)-PRDM16(2), Read Counts 59320, oncomine Variant ClassFusion, Oncogene/Gain-of –function ,variant ID RUNX1-PRDM16.R3P2. Clinically relevant actionable mutations were found in NPM1 and DNMT3a gene of the subject, Fusion transcripts for BCR/ABL1 and RUNX1/PRDM16 were detected.

Discussion

To the best of our knowledge, this is the only case of AML with concomitant BCR-ABL , RUNX1/PRDM16 rearrangement and NPM1 & DNMTamutation have been reported so far [41]. In clinical practice, the distinction between de novo BCR-ABL +ve AML and CML-BP is still challenging [42, 43]. In the present case, patient clinical features (no history of previous hematologic disorders, lack of basophilia, mild hepatomegaly, and a lower bone marrow myeloid/erythroid ratio [14]) and molecular abnormalities (concomitant presence of NPM1 ,DNMTmutations and RUNX1/PRDM 16 rearrangement) were more suggestive of a de novo AML rather than of CML-BP. An additional peculiarity detected in leukemic cells of our patient is the presence of a complex rearrangements and mutations, aberration previously unreported in either AML or CML.

BCR-ABL seems to cooperate with several AML-specific aberrations, including CBFB-MYH 11 and NPM1, although the precise molecular interaction among the altered proteins remains poorly understood [44].

In our case, analysis of NPM1 and BCR-ABL detected in both instances a high transcript copy number. Together with the elevated number of metaphases harboring the Philadelphia chromosome , these findings suggest that the two molecular aberrations were present within the same leukemic clone rather than occurring in two separate clones. However, in recently reported patients with Ph-positive AML, targeted treatment with TKIs was able to abrogate the BCR-ABL +ve clone but did not lead to complete hematologic response, indicating that the BCR-ABL lesion was present at the subclonal level[45]. This highlights the more complex clonal architecture of Ph-positive AMLs as compared to CML. In addition, BCR-ABL has been described only occasionally as a minor subclone arising during AML progression.

At the moment, there is no standardized treatment for patients with Ph-positive AML although few case reports suggested a favorable response to TKIs but still it is investigational[46]. According to the updated ELN criteria, the presence of BCR-ABL fusion gene classifies AML in the adverse risk category while NPM1 mutation is generally regarded as a favorable prognostic in absence of the FLT3-ITD aberration presence of additional abbretions further give out case a very poor prognosis, which was accordingly conveyed to patient.Patient was further told the importance of allogenic bone marrow transplant and he should proceed with HLA testing of family members to undergo the procedure. Patient declined the option of BMT even after informed consent . This case report highlights the possibility to concomitantly detect these two alterations in rare cases of AML and emphasizes the importance of including BCR-ABL screening in routine AML diagnostic panel along with other know mutations like DNMT3A, RUNX1,

NPM1and importance of getting cytogenetics and next generastionsequencing in order to better assign the patient to the correct risk category and targeted treatment.

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 have no information about the mutational status of the CP,[47] whereas double mutated NPM1 BCR-ABL1+ AML, although rare and even rarer is presence of RUNX1-PRDM16 and DNMT3A aberrations being concomitantly present ,clearly shows here we are dealing with denovo AML . 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..

Beyond first-line treatment of AML, the use of TKI remains an individual decision, both in combination with intensive chemotherapy and/or as a bridge to allogeneic stem cell transplantation. In each single case, potential benefits have to be weighed against potential risks.since there are no antecedents to guide us, we rather play safe continuing a course of action that should be highly effective and with affordable side effects so far for every patient.

As the patients identified with these kind of rare of the rare mutations in AML , researchers all over the world should come around to prepare a data base to identify , classify and treat accordingly so that in coming days we have uniform guidelines to best possible manage such rare clinical scenarios and give best treatment and management to our worthy patients.

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