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Acute Lymphoblastic Leukemia to Acute Promyelocytic Leukemia: phenotype switch at relapse. A Case Report

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Abstract

Lineage switch in acute leukemias is considered a rare event, especially in what concerns adult disease compared to pediatric patients. Differential diagnosis between biphenotypic/bilineal leukemias, de novo leukemias, therapy-related and phenotype switch variants, stands as an intricate challenge. Complementary laboratory studies and complex laboratory assays (conventional karyotyping, FISH- fluorescence in situ hybridization, molecular biology, immunophenotyping, etc.) represent one of the crucial resources regarding the process of establishing an accurate diagnosis, thus having a firm ground for the most beneficial treatment choice. Aim: To emphasize the diagnostic and therapeutic particularities regarding the case of a female patient with acute lymphoblastic leukemia (ALL) who later developed a phenotype switch towards an intermediary form of acute myeloid leukemia (AML), sharing features of both AML with maturation and atypical acute promyelocytic leukemia (AML M2/M3/APL).

Material and methods: *We hereby present the case of a 66 year old female, diagnosed with B- ALL, who underwent both classical chemotherapy (adequate protocol related to age, genetic profile, commorbidites) and bispecific monoclonal antibody therapy at first early relapse (Blinatumomab), followed by phenotype switch at second early relapse towards atypical APL. Combined ATRA and anthracycline therapy followed, yet laboratory work-up shows refractory disease. Complications during treatment were comprised of severe DIC (disseminated intravascular coagulation) and infections- sepsis followed by exitus. Results and conclusions: This is the case of a phenotype switch in a patient with ALL, who underwent both classical chemotherapy and Blinatumomab, towards myeloid lineage- refractory APL atypical variant. Availability of flow cytometry and cytogenetics during morphology evaluation represents a key aspect in the management of such hematologic malignancies.*

Keywords: acute lymphoblastic leukemia, acute promyelocytic leukemia, phenotype switch, bispecific monoclonal antibody, chemotherapy, flow cytometry.

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Case Report

A 66 year old female, with unremarkable personal and familial medical history and no apparent exposure to toxic environment, presents in June 2019 with anemia related symptoms (fatigue, loss of appetite, chest pain, heart palpitations) and unintentional weight loss.

Ambulatory laboratory work-up showed a full blood count (FBC) with normocytic normochromic anemia, moderate thrombocytopenia, leukocytosis and monocytosis (haemogloblin 9.6 g/dl, platelets 50.000/mmc, leukocytes 11980/mmc and 6480/mmc monocytes). Biochemistry work-up revealed elevated LDH (1026 u/l) and moderate elevation of markers indicative of systemic inflammation. It should be noted that serologies for HIV, hepatic B and C viruses were negative.

Persistence of symptoms and laboratory work-up anomalies prompted further evaluation, thus a peripheral blood smear (PBS) was obtained, which showed 32% blasts with the following description: agranular blastic cells, with a large round nucleus, regular or reniform, with a central disposition, fine chromatin (gigantic nucleolus) and scant basophilic cytoplasm.

Further on, a bone marrow aspiration was obtained, revealing a hypercelullar marrow with frequent blastic cells, small or medium-sized, agranular or with rare azurophilic granules, with a large round nucleus, basophilic cytoplasm, occasional cytoplasmic vacuoles, summing up approximately 38% lymphoblasts.

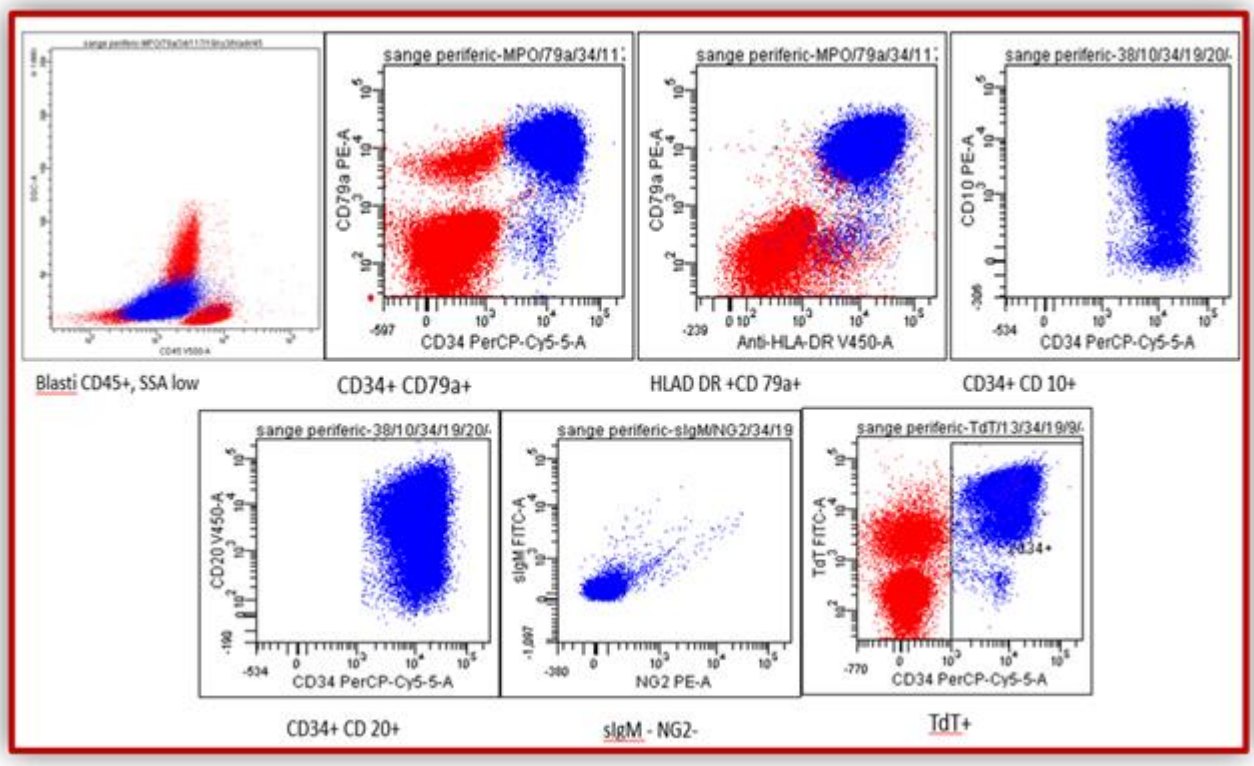

Fig.1: Flow cytometry panels at presentation: ALL B common B phenotype; positivity for CD34 and B markers (CD10, CD19, CD79a, CD20), negativity for surface IgM and NG2.
Courtesy of Hematology Laboratory of Coltea Hematology Clinic.

In order to identify the precise subtype, **immunophenotyping/flow cytometry** followed (obtained from peripheral blood, as a subsequent bone marrow aspiration resulted in dry tap and insufficient sample material for adequate preparation), **which concluded the following phenotypic profile:** 57% **ALL B common** B phenotype blasts, CD19+, CD34+, cyCD79a+, cyCD22+, CD10+, CD20+, CD38+, HLA DR+, TdT+, with aberrant expression of myeloid markers CD66c (72%) and CD 33 (47%) (seen on the CD19+ CD34+ population) (Fig.1).

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Cytogenetics analysis revealed **normal female karyotype and molecular biology showed negative BCR-ABL1** transcript. Other molecular patterns, which carried prognosis stratification importance, were negative (including MLL gene rearrangements, now known as KMT2A rearrangements with different fusion partners).

Pretreatment evaluation also included an abdominal ultrasound- which revealed the spleen sized 15 cm long axis and an echocardiography- with normal left ventricle function and 60% ejection fraction.

A specific induction protocol was started in late August 2019, adapted to the patient's age and to the cytogenetic, phenotypic and molecular characteristics of the disease: B ALL, BCR: ABL1 negative (induction protocol for Philadelphia chromosome negative ALL >60 years old, GRAALL). Along the induction phase, the patient went through therapy and disease related complications, such as infections and DIC, which required administration of large spectrum antibiotics, antifungals and blood products such as fresh frozen plasma (FFP) and cryoprecipitate (CPP). An interesting aspect regardind the DIC was its severity and slow favorable evolution despite correct management (with extremely low fibrinogen values < 80 mg/dl). It should be noted that ATIII, aPTT and PT work-up showed normal values.

Bone marrow aspirate re-evaluation showed no lymphoblasts, thus proving disease chemosensitivity, with normal aspect and maturation of the other lineages. MRD (minimal residual disease) assessment followed, showing <5 % lymphoblasts in the bone marrow, but it should be noted that MRD sample was obtained before the end of the induction phase.

For CNS involvement assessment, a lumbar puncture was performed and intrathecal therapy was administered after (with previous exclusion of intracranial hypertension through fundoscopic exam- ophtalmoscopy and neurological exam). CSF analysis revealed absent CNS disease.

Thus, in november 2019 the pacient achieved complete remission and consolidation therapy followed, with constant bone marrow evaluation.

June 2020 brings forth **the first disease relapse (1st early)**, with a FBC showing 27000 leukocytes/mmc and 12000 monocytes/mmc. A PBS was obtained again, showing 56% blasts and bone marrow aspiration revealed 90% infiltration comprised of lymphoblasts; **flow cytometry confirmed the initial phenotype,** thus reinduction with dexamethasone and Blinatumomab was started, according to national and international guidelines/protocols. It should be noted that DIC was present with similar intensity as previously seen (at disease onset). CSF analysis was performed revealing absent CNS disease, along with intrathecal therapy after.

During the second cycle with Blinatumomab, the patient developed severe neurological toxicity- 3rd grade evolving towards 4th grade (starting from intense bilateral upper extremities tremor and reaching loss of consciousness with a GCS score of 9 and desaturation). Administration was, therefore, discontinued and the patient recovered, following corticotherapy and admission to ICU.

Another bone marrow evaluation showed favorable response, with no lymphoblasts. Maintenance therapy followed, with constant BM evaluation that showed remission. The patient was informed regarding the prognosis and the implications of allogeneic HSCT procedure (hematopoietic stem cell transplant) but she refused undergoing preparation and the procedure itself.

April 2021 brings **another disease relapse (2nd early)**, with a FBC that showed moderate thombocytopenia and a PBS with 6% blasts. **BM aspirate showed 58% leukemic infiltration (myeloblasts and promyelocytes)**, with the following description: *granulocytic lineage with inhibition of maturation, frequent blastic cells- agranular or granular, with a round nucleus, regular or irregular, visible nucleoli (1-2), frequent cytoplasmic inclusions with a spheric appearance- Auer bodies, frequent atypical promyelocytes with Auer bodies, some with folded nucleus or with visible Auer bodies that overlap the nucleus and also promyelocytes with absent Auer bodies, multiple morphlogical anomalies which cannot establish a certain FAB diagnosis, correlation with cytogenetics and molecular exam is required.*

A primary conclusion based on morphology would have been the presence of an intermediary form between AML M2-M3 FAB or an atypical form of APL, as a presumptive diagnosis.

We also performed a bone marrow biopsy, the imprint showing 26% myeloblasts with similar characteristics previously described, 58% atypical promyelocytes and Auer bodies.

Cytogenetics analysis showed an inconclusive 3R2V pattern (FISH) without a corresponding known transcript and classic karyotype analysis showed multiple anomalies- hyperploidy, translocations, inversions, deletions and duplications, dicentric chromosomes, meaning a complex karyotype, but without any possibility to determine a certain pattern/formula.

Molecular biology showed negativity for PML::RARA, RUNX1-RUNX1T1, CBF-MYH11.

Regarding flow cytometry, the determined phenotype consisted of 79% abnormal population with multiple phenotypic anomalies, AML- M2 aspect (with maturation), however, the presence of weak positive CD15, HLA DR negative blasts and other phenotypic features (including some CD34 negative blasts) also point towards APL entity (Fig.2 and Fig.3).

Of important note, the samples and specimens for flow cytometry, cytogenetics and molecular biology were analysed by two different institutions with solid experience in the field of hematologic malignancies.

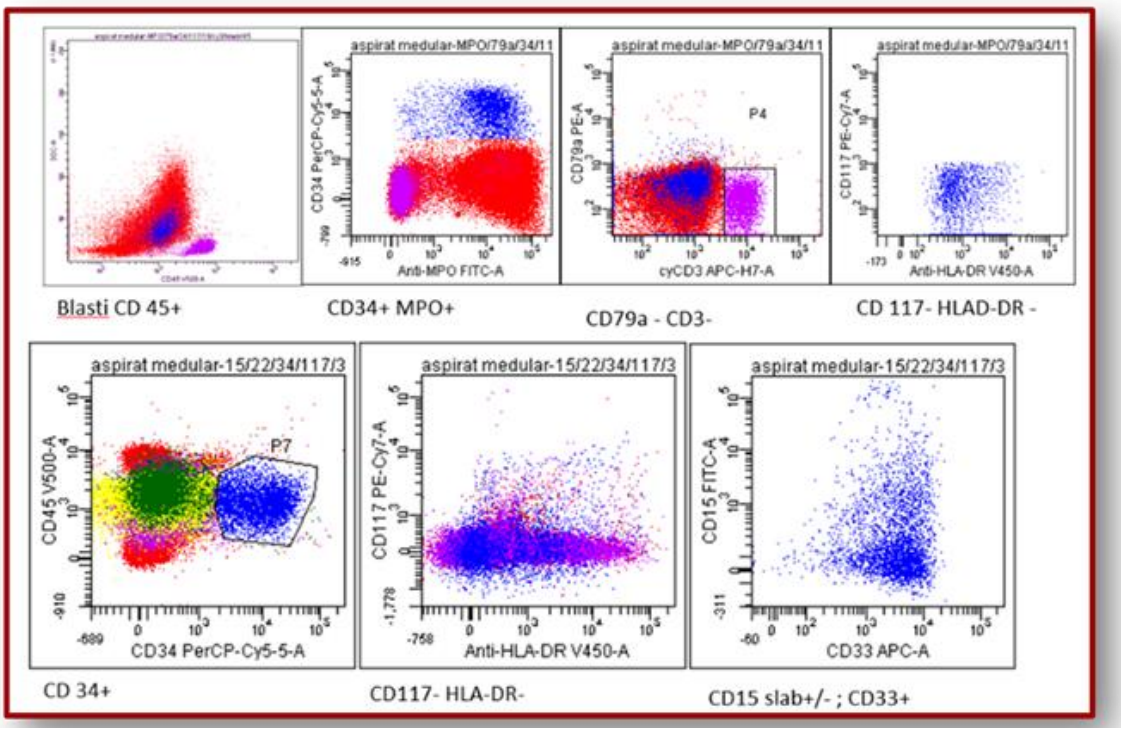

Fig. 2: First bone marrow aspirate at 2nd disease relapse- flow cytometry panels; switch towards AML/APL variant. Notice the absence of B/T markers, positive MPO, weak positive CD15, positive CD33, negative CD117, mostly negative HLA DR blast population. Courtesy of Hematology Laboratory of Coltea Hematology Clinic.

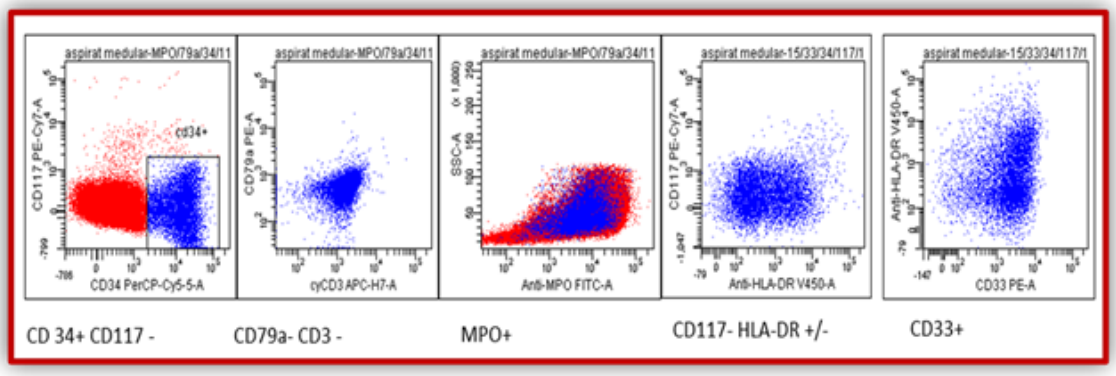

Fig.3: Second bone marrow aspirate at 2nd disease relapse- flow cytometry panels; switch towards AML/APL variant. Notice absence of B/T markers, MPO and CD33 positivity, CD117 negativity, both positive and negative HLA-DR blast population. This result was based on the analysis of two bone marrow aspirate specimens obtained 7 days apart. Courtesy of Hematology Laboratory of Coltea Hematology Clinic

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The therapeutic approach consisted of induction therapy with ATRA (all-trans-retinoic acid), idarubicin and cytarabine, with appropriate ATRA differentiation syndrome prophylaxis- corticotherapy and supportive care. Unfortunately, the PBS showed constant presence of myeloblasts and atypical promyelocytes despite treatment (25% myeloblasts, 12% promyelocytes respectively), proving refractory disease. Also, DIC was present, even more severe than previous presentations- prolonged mucocutaneous bleeding (extensive hematomas at the site of venipunctures, also on the posterior thorax and lumbar region, following bone marrow biopsy and aspiration procedures) which did not respond to hemostatic agents and blood products. Pulmonary infection followed, which developed into severe sepsis and eventually exitus.

Discussions

Acute lymphoblastic leukemia (ALL) represents a malignant lymphoid disease that has its origins in a B or T lymphocyte progenitor. Consecutive proliferation and accumulation of clonal cells in the bone marrow will eventually lead to the supression of hematopoiesis, followed by pancytopenia (anemia, thrombocytopenia, neutropenia). A challening aspect in the course of the disease is the possibility of CNS involvement and also involvement of extramedullary sites such as the gonads, thymus, liver, spleen and lymph nodes. It has many subtypes and its classification is based on morphologic, immunologic, cytogenetic and molecular characteristics. Often, leukemia and lymphoma can overlap (lymphoblastic leukemia/ lymphoma) and can be a clinical form of presentation of the same disease. (1), (2)

B cell ALL is considered to be more frequent in the pediatric population, given the fact that almost three quarters of cases occur in children aged < 6 years old, with predominance regarding the male sex. In what concerns the adult, the peak of incidence is considered somewhere past the age of 60 years old, even though the recent clinical experience of past years has brought significant variations. (2)

On the other side, acute promyelocytic leukemia (APL) is a distinct variant of acute myeloid leukemia (AML), a hematopoietic neoplasia restricted to cells which belong to the myeloid lineage; it can occur at any age and constitutes aproximately 7% of AML cases. Classified as AML- M3 in the FAB classification system (French-American-British), it currently stands as acute promyelocytic leukemia with t(15;17)/PML::RARA. It is considered a medical emergency, due to specific acute complications caused by DIC- disseminated intravascular coagulation, which carry serious hemorrhagic risks. Usually, treatment should start even before there is cytogenetic and molecular confirmation, on the basis of cytologic aspects/criteria. However, multiple variant translocations involving RARA gene have been described. (3), (4)

Lineage switch is usually a phenomenon seen following certain type of therapies or at relapse and mostly in cases that carry specific aberrations such as t(4;11)/ KMT2A/AFF1 fusion protein (formerly known as MLL/AF4). (5)

We considered this to be the case of a phenotype switch in a patient with B ALL (common B), who underwent classical chemotherapy followed by Blinatumomab (bispecific monoclonal antibody; immunotherapy targeted at CD19 and also having a CD3 binding site for T cells), towards AML- specifically atypical refractory APL. The key points/aspects that led to this diagnosis were mainly based on the bone marrow morphology, flow cytometry and also the clinical evolution- severe DIC with severe mucocutaneous bleeding.

It is well known that Blinatumomab therapy can play a role in inducing phenotype switch at relapse. However, the majority of current journal articles and case reports focus mostly on the pediatric population, because lineage switch is much more frequent in this category. In the adult category there are few reported cases of B-ALL regarding phenotype switch after bispecific monoclonal antibody therapy. (6), (7), (8)

Also, the majority of available studies were conducted on ALL positive for KMT2A/AFF1 mutation, known for its unfavorable prognosis and for being amongst the ones associated with phenotype switch at relapse. (8), (9)

The mechanism of switch induction is still unclear, with many debating on the matter. Taking a closer look at the present case, we can conclude that Blinatumomab was indeed efficient, given the fact that at relapse (2nd), flow cytometry and other complex complementary laboratory assays didn't detect any CD19 positive B-ALL blasts. However, expanding our perspective, we have to ask ourselves where did the newly emerged AML blasts come from. It is important to notice that the AML blasts lacked CD19 expression, this being one of the reasons they could escape Blinatumomab cytolytic effect. Also, this points towards another hypothesis: clones from both lineages could have been present all along, and after treatment, one of them could have been selectively suppressed. However, flow cytometry at first relapse failed to identify a separate, distinct AML subclone (there is still debate on its

sensitivity). Therefore, we still consider this to be the case of a phenotype switch that took place after Blinatumomab therapy. (10)

Another aspect that holds significant importance is that the loss of CD19 antigen is not sufficient for switch induction- lineage reprogramming is the driver key towards phenotype switch. (10), (11)

In what concerns immunotherapy resistance mechanisms, multiple theories have been proposed, some of them pending approval and demonstration in on-going studies. One of the most highlighted mechanism of resistance is the downregulation of CD19 antigen. There have been studies able to identify emergent CD19 negative clones only after 2 cycles of Blinatumomab therapy (with complementary flow cytometry assays to check if commonly used flow cytometry antibodies competed with Blinatumomab bound to CD19). (12)

Another mechanism regarding resistance consists of upregulation of PD-L1 (programmed death ligand 1) in tumor cells. On the other side, anti-tumor activity (endogenous) leads to upregulation of PD 1 on T cells, which eventually leads to T cell anergy and consequently suppression of immunity (through the PD1-PD-L1 pathway, known to bear responsibility for tumor cells immune escape). Thus, T cells activated by Blinatumomab won't exhibit the same anti-tumor response because of the PD1- PD-L1 enhanced pathway of T cell inhibition (through modulation of T cell activity). Also, it appears that bispecific molecules usage can result in T cell exhaustion by continous exposure, given its regimen of infusion. Therefore, many implications have surfaced regarding the concomitant usage of immune check-point inhibitors such as Pembrolizumab or Nivolumab (that bind to PD1 and prevent its binding to PD-L1), taking into consideration their mechanism of action which has, as main purpose, activation of T cells. This could be a reliable solution to actively targeting resistance mechanism to bispecific molecules. (13), (14), (15), (16)

Neurotoxicity from Blinatumomab can range from mild symptoms to serious adverse reactions, i.e from a mild headache, tremor, confusion, to disorientation, ataxia, seizure, aphasia and even coma/stupor. The mechanism that stands behind this is usually attributed to activated T cells that can disrupt the blood-brain barrier. Consequently, the bispecific molecule can bind to CD19 positive cells in the CNS and cause cytokine release. It is considered that patients with actual CNS involvement may be at greater risk of severe neurotoxicity, but also, given the fact that there is a variable expression of CD19 in the CNS, there could be subsets of patients more affected by the adverse neurological side effects. These manifestations occured more frequently during the first 7 days of infusion in most clinical trials and most of them have been resolved with the use of corticotherapy and cessation of administration. (17), (18), (19)

Another cause of concern regarding neurotoxicity is represented by tumor burden before Blinatumomab therapy and its correlation with the amplitude of adverse reactions. Many studies have brought in full sight the idea that bispecific molecules could be of more use in what concerns efficacy and safety it they were administered in frontline therapies and not necessarily at relapse. Also, it is generally accepted that prephase with corticosteroids is mandatory when patients present with more than 50% bone marrow blasts and more than 15000 monocytes/mmc (blasts)- which was also the case concerning our patient at 1st disease relapse. Moreover, elevated LDH contributes to the proof of a rapidly advancing disease with unpredictable course of progression. All these aspects could suggest that the higher the tumour burdern, the greater the risk of cytokine release syndrome and other severe side effects when using bispecific molecules. (20), (21), (22)

Another aspect of discussion is the presence of aberrrant myeloid markers, which represent a frequent anomaly encountered in ALL. One of the most common myeloid antigen present in available studies was CD13, followed by CD33. There is contradictory data regarding prognosis value and outcome impact. Some studies found the presence of myeloid markers to be of unfavorable prognostic value, while others attested no difference in outcome and survival in patients with aberrant imunophenotype characteristics. However, presence of myeloid aberrant markers has been more frequently seen in Philadelphia chromosome-positive ALL, both in the pediatric and the adult population. (23), (24), (25)

An intricate challenge brought by these phenotypic anomalies is making an accurate differential diagnosis between biphenotypic and bilineal (mixed phenotype) acute leukemia. Biphenotypic leukemia is defined when blasts express myeloid and lymphoid antigens concomitantly in a single blast population, with a score of at least 2 points in the EGIL criteria for biphenotypic leukemia (European Group for Immunological Characterization of Acute Leukemia), meaning that MPO (myeloperoxidase- major myeloid antigen) and another major antigen of other lineage- either B or T cell origin, should be present. Bilineal leukemia, on the other side,

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refers to a hematopoietic malignancy when blasts cannot be classified as either myeloid or lymphoid, or when blasts from both lineages are present (two or more distinct blast populations). All in all, the principle of reciprocal intensity of myeloid and lymphoid markers applies, flow cytometry being a very useful tool in assessing this complex diagnosis. (24), (26), (27)

Returning to our key event, the phenotype switch towards myeloid lineage, specifically atypical APL, it is important to note that this was a diagnosis established through a correlation between clinical evolution and complementary laboratory data. Taking into consideration that it was not a typical case of a PML::RARA positive APL- not manifesting the specific chromosomal translocation t (15;17), the criteria that hold this diagnosis were the DIC, the morphological aspect and the flow cytometry characteristics.

It is known that there are cases of APL due to variant translocations (with different fusion partners for RARA gene), with similar morphologic features as the classic form of APL. However, a rare form of APL (less than 1%), specifically ZBTB16-RARA t(11;17), holds both AML M2 and M3 features (including sometimes low granulation or absence of typical bilobed nucleus), showing an intermediary aspect on bone marrow aspirates- which was also described in our case report. Interestingly, it is considered a refractory form, showing lack of differentiation to retinoids and also severe, hardly manageable DIC. Usually, cytogenetics analysis (FISH studies and karyotype analysis) should be able to determine the presence of such variant- but our patient had a complex karyotype at 2nd disease relapse, without possibility to determine the exact formula (on multiple subsequent evaluations). Also, even though an intensive AML induction regimen was administered, along with ATRA, no significant improvement was observed. There are few cases reported carrying this specific mutation where complete remission was achieved at a second reinduction along with ATRA administration, followed by maintenance therapy with ATRA. Unfortunately, we didn't achieve the same result in our patient. Still, it should be brought to attention that this is the case of an APL diagnosed at relapse from B-ALL and not the novo APL without a prior diagnosed malignancy. (4), (28), (29), (30)

Conclusions

This is the case of a phenotype switch in a patient diagnosed with B ALL- common B, who underwent both classical chemotherapy and bispecific monoclonal anitbody therapy- Blinatumomab, towards AML-refractory atypical APL variant.

The key points that stand firm regarding this diagnosis are the bone marrow morphology, the bone marrow aspirate flow cytometry, the clinical evolution and outcome (severe DIC with severe mucocutaneous bleeding). Secondary AML was not considered a feasible diagnostic option, given the early relapse and the absence of dysplastic elements on repeated bone marrow examinations (both during consolidation and maintenance therapy).

Once again it has been proven that laboratory techniques and quality assays are extremely valuable, mandatory and necessary in what concerns establishing an accurate diagnosis in hematology, as they can dictate the course of medical action taken by the clinician.

Abbreviation list

ALL- acute lymphoblastic leukemia
AML- acute myeloid leukemia
APL- acute promyelocytic leukemia
ATRA- all trans retinoic acid
BM- bone marrow
CPP- cryoprecipitate
DIC- disseminated intravascular coagulation
EGIL- European Group for the Immunological Classification of Leukemia
FAB classification system- French-American- British classification system
FBC- full blood count
FISH- fluorescence in situ hybridization
FFP- fresh frozen plasma
GRAALL- Group for Research on Adult Acute Lymphoblastic Leukemia
LDH- lactic acid dehydrogenase/ lactate dehydrogenase
MPO- myeloperoxidase
PBS- peripheral blood smear
PD1- programmed cell death protein 1
PD-L1- programmed cell death ligand 1

Conflict 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.

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Nil

References

1. Kenneth Kaushansky, Marshall Lichtman, Josef Prchal, Marcel Levi, Oliver Press, Linda Burns, Michael Caligiuri. Williams Hematology, 9th ed./ Part XI: Malignant Lymphoid Diseases. s.l.: © 2016, by McGraw-Hill Education, New York.
2. Anjali S Advani, MDJon C Aster, MD, PhD. Clinical manifestations, pathologic features, and diagnosis of B cell acute lymphoblastic leukemia/lymphoma. s.l.: UpToDate Inc., www.uptodate.com, Oct 2023.
3. Kenneth Kaushansky, Marshall Lichtman, Josef Prchal, Marcel Levi, Oliver Press, Linda Burns, Michael Caligiuri. Williams Hematology, 9th ed./Part X: Malignant Myeloid Diseases. s.l.: © 2016, by McGraw-Hill Education, New York.
4. Richard A Larson, MDSandeep Gurbuxani, MBBS, PhD. Clinical manifestations, pathologic features, and diagnosis of acute promyelocytic leukemia in adults. s.l. : UpToDate Inc., www.uptodate.com, Oct 2023 (literature review current through)/topic last updated: Sep 20, 2022.
5. Haddox, C., Mangaonkar, A., Chen, D. et al. Blinatumomab-induced lineage switch of B-ALL with t(4:11)(q21;q23) KMT2A/AFF1 into an aggressive AML: pre- and post-switch phenotypic, cytogenetic and molecular analysis. s.l. : Blood Cancer J. 7, e607 (2017)/https://doi.org/10.1038/bcj.2017.8.
6. Semchenkova, A., et al. Lineage Conversion in Pediatric B-Cell Precursor Acute Leukemia under Blinatumomab Therapy. s.l.: Int. J. Mol. Sci. 2022, 23, 4019/https://doi.org/10.3390/ijms23074019.
7. Brittany M. Lee, Corinne Summers, Karen M. Chisholm, Sandra D. Bohling, Kasey J. Leger, Rebecca Gardner, Colleen Annesley, Adam J. Lamble. Plasticity of lineage switch in B-ALL allows for successful rechallenge with CD19-directed immunotherapy. s.l. : Volume 7, Issue 12, 2023, ISSN 2473-9529; https://doi.org/10.1182/bloodadvances.2022009480.
8. Matthias Wölfl, Mareike Rasche, Matthias Eyrich, Renate Schmid, Dirk Reinhardt, Paul G. Schlegel. Spontaneous reversion of a lineage switch following an initial blinatumomab-induced ALL-to-AML switch in MLL-rearranged infant ALL. s.l.: Blood Adv (2018) 2 (12): 1382–1385/ /https://doi.org/10.1182/bloodadvances.2018018093.
9. Rui R. He, Zacharia Nayer, Matthew Hogan, Raymund S. Cuevo, Kimberly Woodward, David Heyer, Christine A. Curtis and Jess F. Peterson. Immunotherapy-(Blinatumomab-) Related Lineage Switch of KMT2A/AFF1 Rearranged B-Lymphoblastic Leukemia into Acute Myeloid Leukemia/Myeloid Sarcoma and Subsequently into B/Myeloid Mixed Phenotype Acute Leukemia. s.l. : Case Reports in Hematology, vol. 2019, Article ID 7394619, 4 pages, 2019. https://doi.org/10.1155/2019/7394619.
10. Haddox, C., Mangaonkar, A., Chen, D. et al. Blinatumomab-induced lineage switch of B-ALL with t(4:11)(q21;q23) KMT2A/AFF1 into an aggressive AML: pre- and post-switch phenotypic, cytogenetic and molecular analysis. s.l. : Blood Cancer J. 7, e607 (2017). https://doi.org/10.1038/bcj.2017.89.
11. Liora Schultz and Rebecca Gardner. Mechanisms of and approaches to overcoming resistance to immunotherapy. s.l.: Hematology Am Soc Hematol Educ Program. 2019 Dec 6; 2019(1): 226–232./doi: 0.1182/hematology.2019000018.
12. Friederike Braig, Anna Brandt, Mariele Goebeler, Hans-Peter Tony, Anna-Katharina Kurze, Peter Nollau, et.al. Resistance to anti-CD19/CD3 BiTE in acute lymphoblastic leukemia may be mediated by disrupted CD19 membrane trafficking. s.l.: Blood (2017) 129 (1): 100–104./https://doi.org/10.1182/blood-2016-05-718395.
13. Köhnke T, Krupka C, Tischer J, Knösel T, Subklewe M. Increase of PD-L1 expressing B-precursor ALL cells in a patient resistant to the CD19/CD3-bispecific T cell engager antibody blinatumomab. s.l. : J Hematol Oncol. 2015 Oct 8;8:111. doi: 10.1186/s13045-015-0213-6. PMID: 26449653; PMCID: PMC4599591.
14. Middleton, Winston M. Zhu and Mark R. Combination therapies for the optimisation of Bispecific T-cell Engagers in cancer treatment. s.l.: Immunotherapy Advances, 2023, 3, 1–11/https://doi.org/10.1093/immadv/ltad013
15. Mark Wunderlich, Nicole Manning Christina Sexton Eric O'Brien Luke Byerly Cody Stillwell John P. Perentesis, James C. Mulloy, Benjamin Mizukawa. PD-1 Inhibition Enhances Blinatumomab Response in a UCB/PDX Model of Relapsed Pediatric B-Cell Acute Lymphoblastic Leukemia. s.l.: Front. Oncol., 13 April 2021, Sec. Cancer Immunity and Immunotherapy, Volume 11 - 2021 | https://doi.org/10.3389/fonc.2021.642466.
16. Nora Philipp, Maryam Kazerani, Alyssa Nicholls, Binje Vick, Jan Wulf, Tobias Straub, et. al. T-cell exhaustion induced by continuous bispecific molecule exposure is ameliorated by treatment-free intervals. s.l.: Blood (2022) 140 (10): 1104–1118. IMMUNOBIOLOGY AND IMMUNOTHERAPY| SEPTEMBER 8, 2022.
17. Lindsey Hathaway, Jeremy Michael Sen and Michael Keng. Impact of blinatumomab on patient outcomes in relapsed/refractory acute lymphoblastic leukemia: evidence to date. s.l. : Patient Relat Outcome Meas. 2018; 9: 329–337/doi: 10.2147/PROM.S149420.

18. Litzow, Tania Jain and Mark R. No free rides: management of toxicities of novel immunotherapies in ALL, including financial. s.l.: Blood Adv. 2018 Nov 27; 2(22): 3393–3403/doi: 10.1182/bloodadvances.2018020198.
19. Bhurke, Sheetal. CD19 expression in brain cells may be associated with immunotherapy-related neurotoxicity. Available at: https://lymphomahub.com/medical-information/cd19-expression-in-brain-cells-may-be-associated-with-immunotherapy-related-neurotoxicity#:~:text=CD19%20expression%20in%20brain%20cells%20may%20be%20associated%20with%20immunotherapy%2Drelated%20neurotoxicity. Jan 7, 2021.
20. Śliwa-Tytko P, Kaczmarska A, Lejman M, Zawitkowska J. Neurotoxicity Associated with Treatment of Acute Lymphoblastic Leukemia Chemotherapy and Immunotherapy. s.l.: International Journal of Molecular Sciences. 2022; 23(10):5515. https://doi.org/10.3390/ijms23105515.
21. Cabannes-Hamy A, Brissot E, Leguay T, Huguet F, Chevallier P, Hunault M, et.al. High tumor burden before blinatumomab has a negative impact on the outcome of adult patients with B-cell precursor acute lymphoblastic leukemia. A real-world study by the GRAALL. s.l. : Haematologica 2022;107(9):2072-2080; https://doi.org/10.3324/haematol.2021.280078.
22. Benxia Zhang, Xue Li, Tao Yin, Diyuan Qin, Yue Chen, Qizhi Ma, Pei Shu and Yongsheng Wang. Neurotoxicity of Tumor Immunotherapy: The Emergence of Clinical Attention. s.l.: J Oncol. 2022; 2022: 4259205/doi: 10.1155/2022/4259205.
23. Jeanann L Suggs, Julius M Cruse, Robert E Lewis. Aberrant myeloid marker expression in precursor B-cell and T-cell leukemias. s.l.: Exp Mol Pathol. 2007 Dec;83(3):471-3. doi: 10.1016/j.yexmp.2007.08.012/DOI: 10.1016/j.yexmp.2007.08.012.
24. Miguel E. Cuéllar-Mendoza, Francisco R. Chávez-Sánchez, Elisa Dorantes-Acosta, Blanca M. Arsuaga-Jiménez, and Marta Zapata-Tarrés. Aberrant immunophenotypes in acute lymphoblastic leukemia. s.l.: Permanyer. Boletín Médico del Hospital Infantil de México/Bol Med Hosp Infant Mex. 2020;77(6).
25. Subhajit Hajra, Sathya Panduragan, Prabhu Manivannan, Rakhee Kar, Debdatta Basu. Aberrant antigenic expression in acute leukemia: Study from a tertiary care center in Southern India. s.l.: © 2022 Scientific Scholar on behalf of Journal of Hematology and Allied Sciences/doi: 10.25259/JHAS_26_2021.
26. Kevin E. Shopsowitz, Kalpesh Shah, Hubert Tsui. Lymphoid blasts with aberrant myeloid marker expression and BCR/ABL1: Is it mixed phenotype acute leukemia or B lymphoblastic leukemia? s.l.: WILEY Online Library/Cytometry Part B: Clinical CytometryVolume 102, Issue 1 p. 73-75/https://doi.org/10.1002/cyto.b.22002, 29 March 2021.
27. Nathan J Charles, Daniel F Boyer. Mixed-Phenotype Acute Leukemia: Diagnostic Criteria and Pitfalls. s.l.: Arch Pathol Lab Med 2017 Nov;141(11):1462-1468/DOI: 10.5858/arpa.2017-0218-RA.
28. Xiaoxue Wang, PhD, Jing Wang, MD, and Lijun Zhang, PhD. Characterization of atypical acute promyelocytic leukaemia. s.l.: PMC PubMed Central. Medicine (Baltimore). 2019 May; 98(19): e15537/doi: 10.1097/MD.0000000000015537.
29. Robin T. Dowse, Robin M. Ireland. Variant ZBTB16-RARA translocation: morphological changes predict cytogenetic variants of APL. s.l. : ASH Publications. Blood (2017) 129 (14): 2038/https://doi.org/10.1182/blood-2016-10-743856.
30. Pardo Gambarte L, Franganillo Suárez A, Cornago Navascués J, Soto de Ozaeta C, Blas López C, Atance Pasarisas M, et.al. ZBTB16-RARα-Positive Atypical Promyelocytic Leukemia: A Case Report. s.l. : Medicina (Kaunas). 2022 Apr 6;58(4):520. doi: 10.3390/medicina58040520. PMID: 35454359; PMCID: PMC9027637.