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CASE REPORT

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Mixed phenotype acute leukemia and lineage switch from lymphoblastic leukemia to myeloid leukemia in the course of Philadelphia-negative myeloproliferative neoplasm – case reports and literature review

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Abstract

Philadelphia-negative myeloproliferative neoplasms (Ph-neg MPNs) are characterized by clonal hematopoiesis derived from a mutated hematopoietic stem cell. Ph-neg MPNs rarely transforms into acute leukemia, and in most cases, the transformation leads to the development of acute myeloid leukemia (AML). The incidence of mixed-phenotype leukemia (MPAL) or acute lymphoblastic leukemia (ALL) with lineage switch is much rarer. The unidentified lineage of blast cells is due to the immaturity of their undifferentiated progenitors with co-expression of myeloid and lymphoid antigens. The prognosis of secondary acute leukemia transformed from Ph-neg MPN is very unfavorable, especially in MPAL or lineage switch from ALL to AML cases. Moreover, there are no therapeutic protocols for these specific leukemia subtypes. Therefore, we believe that all cases of MPAL or lineage switch leukemia should be reported. This article presents the case of a patient with JAK2-positive essential thrombocythemia (ET) transformed to MPAL, and a patient with triple-negative primary myelofibrosis (PMF) (negative for *JAK2*, *CALR*, and *MPL*) transformed to ALL with subsequent lineage switch to AML.

Keywords:
mixed-phenotype acute leukemia, acute lymphoblastic leukemia, myeloproliferative neoplasms

Introduction

Philadelphia-negative myeloproliferative neoplasms (Ph-neg MPNs) are characterized by a clonal proliferation of one or more bone marrow cell lineages. MPN arises from the mutation in hematopoietic stem cells resulting in impaired cytokines expression and dysregulation of kinase signaling [1]. Ph-neg MPNs include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF).

The transformation of Ph-neg MPNs into acute leukemia is not very common with varying incidence depending on the Ph-neg MPN subtype. In PMF, the transformation is observed in 20% of patients, while in PV and ET, it is observed in 4% and 1% of patients, respectively [2, 3]. Most commonly, Ph-neg MPN transforms into acute myeloid leukemia (AML). However, there are few reports of transformation into acute lymphoblastic leukemia (ALL) (more than 10 cases published) (Tab. I). However, no reports on the transformation of Ph-neg MPN to mixed-phenotype acute leukemia (MPAL) and lineage switch from ALL to AML were published.

MPAL is a specific type of leukemia in which blasts co-express antigens from more than one cell lineage [2] can be difficult to diagnose. MPAL diagnostics is based on the guidelines of European Group for Immunological Classification of Leukemia (EGIL) [3] and the WHO 2016 classification of myeloid neoplasms and acute leukemia [4]. Leukemias with lineage switch observed during therapy should be considered as a separate group [5].

The incidence of MPAL is very low and accounts for approximately 2–5% of all acute leukemias [2]. Lineage switch from ALL to AML is also rare and accounts for approximately 6–9% of relapsed ALL [6, 7]. According to the literature, these leukemias are usually treatment-resistant. However, currently, there are no prospective controlled clinical trials to determine the optimal treatment protocol [5].

This article describes the case of MPAL in a patient with *JAK2*-positive ET and ALL with lineage switch to AML in a patient with triple-negative PMF (for Janus kinase 2 (*JAK2*), calreticulin (*CALR*), myeloproliferative leukemia virus oncogene (*MPL*) mutations).

Case report 1

A 53-year-old female, without significant medical history, has been referred to a hematology outpatient clinic in March 2010

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Table I. List of published cases of MPN transformation to ALL

No.	Authors [ref.]	Primary diagnosis	Secondary diagnosis	Time to transformation
1	Camós et al. [39]	PV	B-ALL	10 years
2	Suzuki et al. [40]	PV	T-ALL	12 years
3	Hilal and Conley [41]	ET	B-ALL	>20 years
4	Woronzoff-Dashkoff and Litz [42]	ET	ALL	Unknown
5	Ohanian et al. [1]	Post-PV PMF	B-ALL	3 years
6	Alhuraiji et al. [43]	ET/PMF	B-ALL	11 years
7	Dunphy et al. [44]	MF	ALL	3 months
8	Bacher et al. [45]	MPD	Pre-T-ALL	18 months
9	Kim et al. [46]	CMPD	Biphenotypic leukemia	Unknown
10	JabbarAl-Obaidi et al. [47]	CMPD	B-ALL	6 weeks
11	Duployez et al. [48]	MPN	ALL	12 months

ALL – acute lymphoblastic leukemia; B-ALL – acute B-cell lymphoblastic leukemia; T-ALL – acute T-cell lymphoblastic leukemia; pre-T-ALL – acute pre-T cell lymphoblastic leukemia; PV – polycythemia vera; ET – essential thrombocythemia; PMF – primary myelofibrosis; MF – myelofibrosis; CMPD – chronic myeloproliferative syndrome; MPN – myeloproliferative neoplasm

due to thrombocytosis (1.5 G/L). After the exclusion of reactive thrombocytosis and myelodysplastic-myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) [4], the patient was diagnosed with *JAK2*(V617)-positive ET.

Over the next 4 years, until July 2014, the patient was treated with hydroxyurea (HU) with good effect: platelet count (PLT) fell to 500–600 G/L. In August 2014, anemia (hemoglobin (Hgb) – 9.2 g/dL) and thrombocytopenia (PLT – 50 G/L) with normal leukocyte count (8.06 G/L) were observed. Physical examination revealed hepatosplenomegaly. The following biochemical parameters were increased: lactate dehydrogenase (LDH) – 420 U/L, C reactive protein (CRP) – 76.1 mg/L, and GGTP 110 U/L. In a myelogram, bone marrow was infiltrated with blast cells (53% of all cells examined). This population had a mixed phenotype: myelo- and T-cell lymphoblastic: CD34+CD13+CD7+cyCD3+CD36+CD33bright+HLA-DR+CD4+CD8-CD5-CD2-CD117-MPO+TdT-CD64-CD71+ (Fig.1).The cytochemical profile was nonspecific. As expected for lymphoblasts, negative peroxidase and lipid reactions were observed. Dispersed, nonspecific esterase staining pattern, typical for myeloblasts, was detected. The strong enzymatic activity of acid phosphatase has distinguished the population of T-cell lymphoblasts. Patient's karyotype was hyperploid, complex, with i(21q) duplication that can be expected both in AML and ALL(57,XX,+1,+2,+2,+dic(6;12)(q27;p13),+der(8)t(8;11)(p11.2;q13),+der(9)t(9;16)(q13;q13),+11,+add(18)(p11.2),+19,+20,+i(21)(q10)x2[17]/46,XX[3]). No *BCR-ABL* fusion gene was found in FISH using locus-specific probes.

Chemotherapy, according to the PALG ALL6 Ph(-) protocol for patients >55 years of age (dexamethasone, vincristine, daunorubicin, and peg-asparaginase), was started in September 2014. Prophylactic central nervous system (CNS)-directed treatment was also implemented. The chemotherapy was complicated with pancytopenia. The follow-up abdominal ultrasound scan from October showed progression of hepatosplenomegaly. The myelogram performed on October 14, 2014, revealed 2.0% of myeloblasts and 11.0% of mature lymphocytes. In cytometry, 2.0% of blasts and positive minimal residual disease (MRD) (1.65%) were observed. Bone marrow immunophenotyping performed on November 3, 2014, showed a significant increase in the percentage of a blast to 10%, with the evolution of the phenotype and a new leukemia aberrant immunophenotype (LAIP) present, that is, cytoplasmic myeloperoxidase (MPO)-positive blasts. The highest frequency of LAIP was 5.96%.

Because of the persistent weakness of the lower limbs, magnetic resonance imaging (MRI) of the brain was performed. Numerous foci in the cranial bones were observed, with no additional information about the nature of the lesions. The patient died in November 2014.

Case report 2

A 50-year-old male was referred to the outpatient clinic in January 2017 due to anemia (Hgb – 10.4 g/dL), thrombocytopenia (PLT – 61 G/L), and splenomegaly (22 cm spleen and 21 cm liver in the abdominal scan). White blood cells (WBC) was normal (4.68 G/L). The patient reported progressive aversion to exercise and periodic subfebrile symptoms, weight loss over 20 kg in 8 months. The patient was hypertensive, with no other concomitant diseases. Triple-negative PMF (*JAK2*V617F, *CALR*, and *MPL*) with complex karyotype 46,XY,t(11;22)(p15;q13)[4]/46,XY,t(11;22)(p15:q13),t(12;22)(q24.3;q11.2)[12]/46,XY,i(9)(q10)[3]/46,XY was diagnosed [1]. Trepanobiopsy showed typical features of the myeloproliferative syndrome (prefibrotic myelofibrosis). International Prognostic Scoring System (IPSS) score was intermediate (2), The Dynamic Prognostic Scoring System (DIPSS) score was 2, and DIPSS-plus score was 3.

The patient was eligible for the ruxolitinib therapy. The treatment was initiated at 5 mg bid, and after 2 months, the dose was increased to 10 mg bid. Initially, an improvement in the patient's general condition was reported with a decrease in the severity of general symptoms, a distinct reduction in the spleen size and an increase in PLT count to 137 G/L were observed. Unfortunately, 3 months after the initiation of the ruxolitinib therapy, the patient's condition was suddenly worsened. Sweats, weakness, and bone

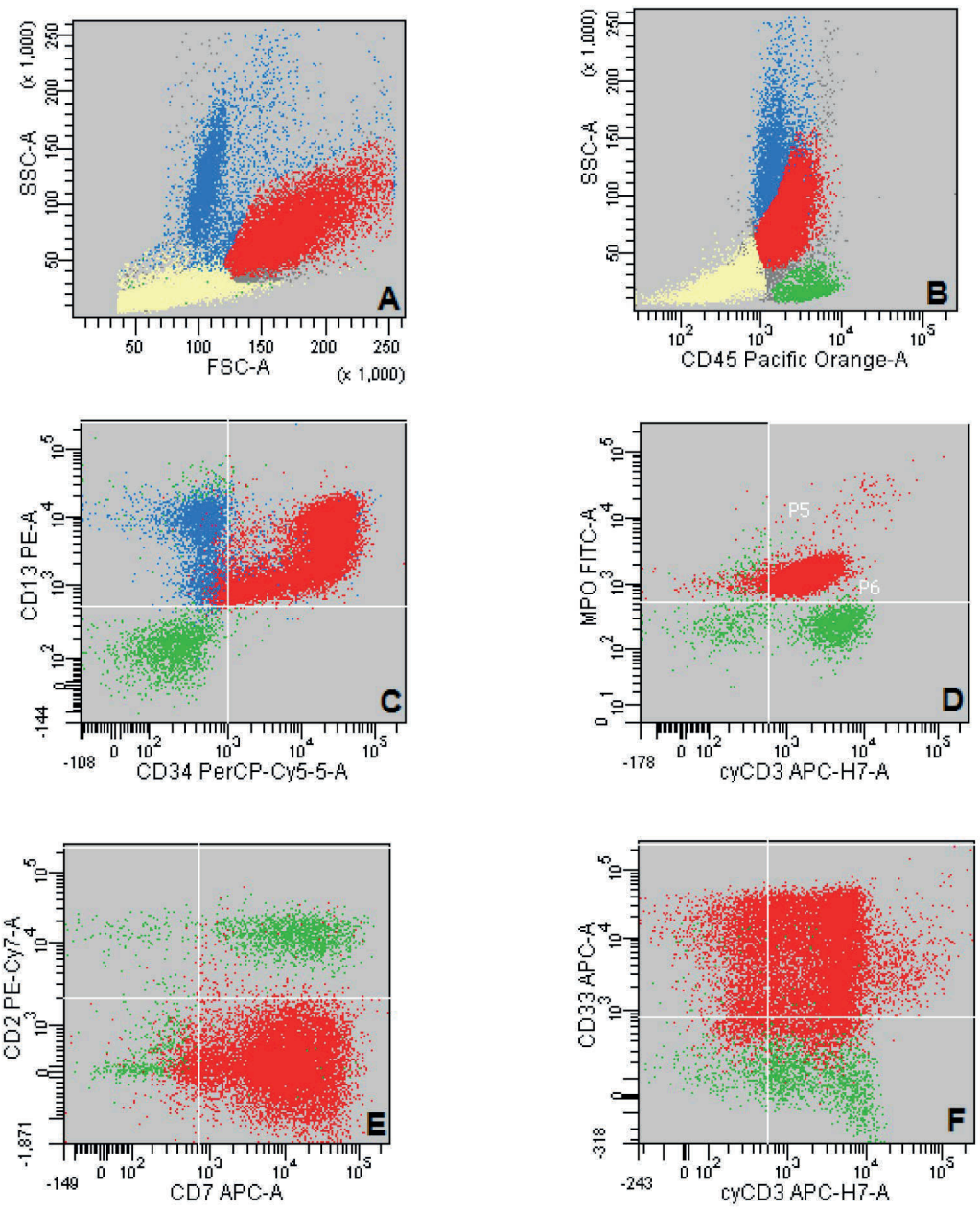

Fig. 1. Cytometric evaluation of the first patient's bone marrow suggesting MPAL

A – subpopulations of bone marrow cells in the FSC/SSC plot: blasts (red), lymphocytes (green), granulocytic cells (blue), and erythroblasts (yellow); B – CD45 vs SSC; C – CD34 vs CD13; D – cyCD3 vs MPO; E – CD7 vs CD2; and F – cyCD3 vs CD33

aches returned. In complete blood count (CBC), leukocytosis (20 G/L), anemia (Hgb – 8.3 g/dL), and thrombocytopenia (PLT < 20 G/L) were observed with hyperuricemia (10.5 mg/dL) and increased LDH (1393 U/L) in the biochemical workup. The progression of hepatosplenomegaly was observed in ultrasound scan (April 2017). The patient was not eligible for the ruxolitinib therapy. In a myelogram, dyserthropoiesis and dysgranulopoiesis were observed. Lymphoblasts constituted 71% of bone marrow cells. ALL was confirmed by immunophenotyping showing 68% of CD45- CD19+ CD34-CD117- HLA-DR+ CD24+ CD10+ TdT+ CD38+ cyCD79a+ cyCD22+ CD9+ CD21- CD33- CD22+ CD20-+ lymphoblasts (Fig. 2). Between May and July 2017, the patient underwent rituximab, cyclophosphamide, vincristine, adriamycin and dexamethasone (R-hyperCVAD) chemotherapy, with a decrease in spleen size from 26 to 22 cm and a decrease in lymphoblast count to 0.2% with positive MRD. In September 2017, the patient had an unknown donor undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT). However, hematopoietic lineages were not regenerated in the bone marrow, and hepatosplenomegaly was shown in a follow-up abdominal scan. The myelogram performed on October 9, 2017 revealed 15% myeloblasts and 19% myeloid blasts CD45dim+CD34-CD117+ MPO- CD33+ CD13+ CD19- CD20- CD38+ CD15+ CD71+ CD10- CD9- HLA-DR-+ (Fig. 3).

In mid-October, an analysis of post-transplant chimerism revealed

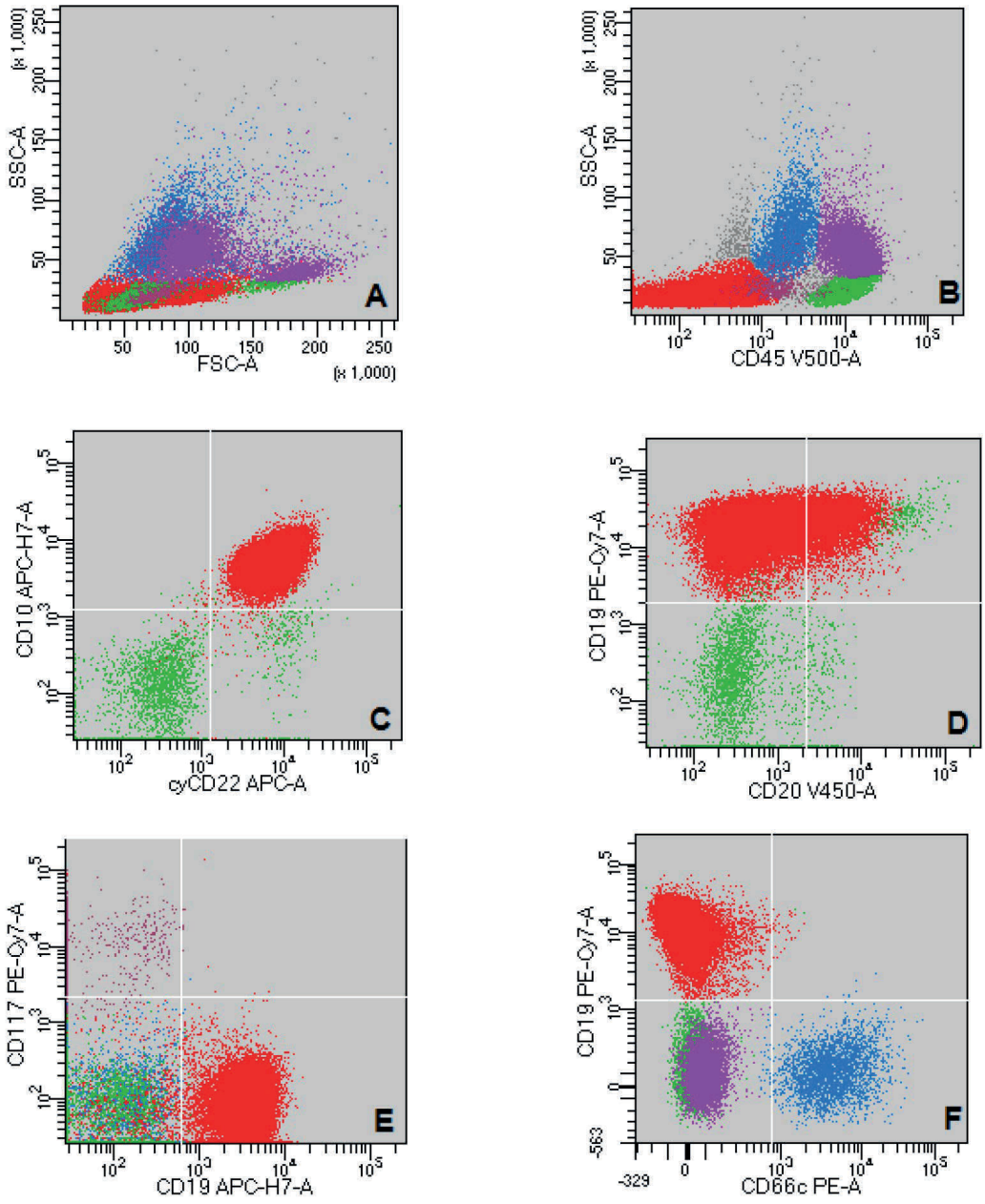

Fig. 2. Cytometric evaluation of the second patient's bone marrow suggesting B-cell precursor acute lymphoblastic leukemia

A – subpopulations of bone marrow cells in the FSC/SSC plot: B lymphoblasts (red), lymphocytes (green), granulocytic cells (blue), monocytes (purple), and myeloblasts (burgundy); B – CD45 vs SSC B CD45- lymphoblasts; C – cyCD22 vs CD10; D – CD20 vs CD19; E – CD19 vs CD117; and F – CD66c vs CD19

90.85% of the autologous cells in the sample. In the follow-up in the outpatient clinic performed at the end of the same month, pancytopenia was observed: WBC – 0.47 G/L, PLT – 6 G/L, Hgb – 6.5 g/dL, neutropenia – 0.07 G/L, lymphocytopenia – 0.16 G/L with CRP – 27.8 mg/L, LDH – 426 U/L, and serum cyclosporine concentration 70.2 ng/mL. In CBC performed at the end of October, 53% of myeloblasts and 21% of mature lymphocytes were observed. Immunophenotyping performed on 26 October 2017, 32% myeloblasts were found. Transformation into AML was diagnosed. The last contact with the patient was in October 2017.

Discussion

AML is the most commonly reported subtype of acute leukemia in the course of Ph-neg MPN. According to the literature, the transformation of Ph-neg MPN into ALL is a very rare phenomenon; no reports were found on the development of MPAL in the course of Ph-neg MPN. Similarly, no cases of the transformation of Ph-neg MPN to ALL with lineage switch to AML after the therapy were described. In contrast to Ph-neg MPN, the lymphoblastic crisis is more common

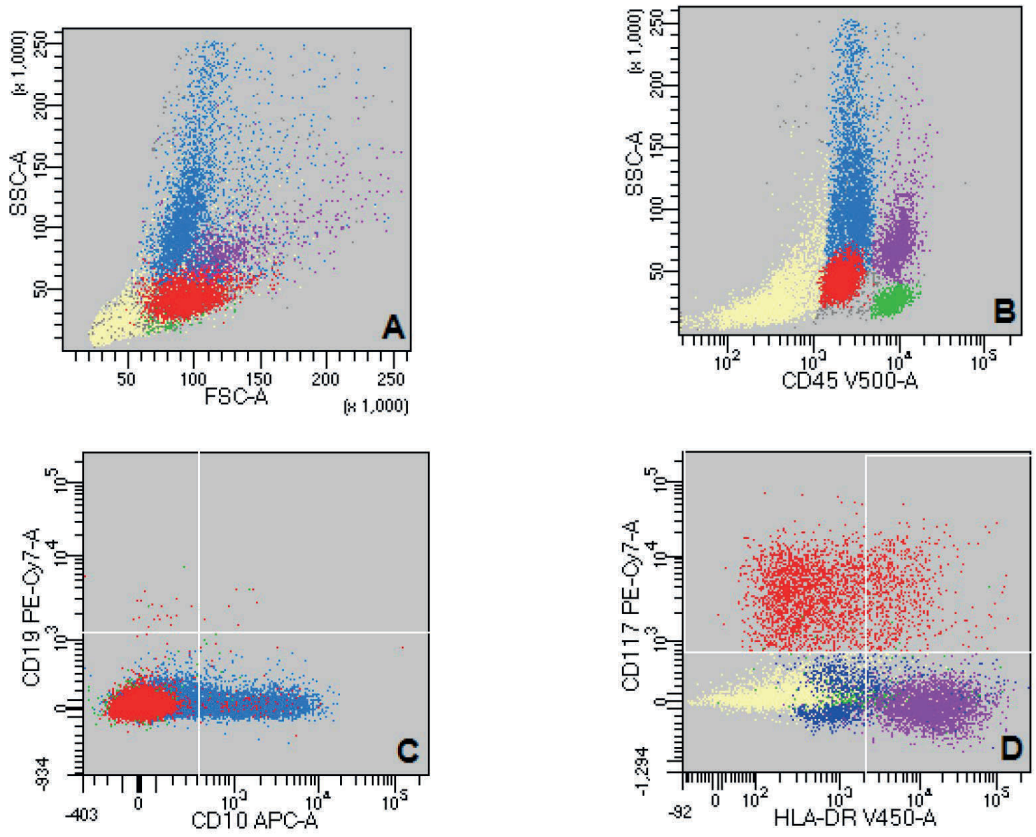

Fig. 3. Cytometric evaluation of the second patient's bone marrow suggesting acute myeloid leukemia

A – subpopulations of bone marrow cells in the FSC/SSC plot: myeloblasts (red), lymphocytes (green), granulocytic cells (blue), monocytes (purple), and erythroblasts (yellow); B – CD45 vs SSC CD45dim + myeloblasts; C – CD10 vs CD19; and D – HLA-DR vs CD117

in the course of chronic myeloid leukemia (CML) [8]. For example, in a study of 31 patients with CML in the blast crisis (BC), 24 patients had myeloblastic and 7 had lymphoblastic disease [9]. CML transformation into biphenotypic leukemia/MPAL [10, 11, 12] and with phenotype switch [13] were also reported.

There are two main theories explaining the development of MPAL and leukemia with lineage switch after the therapy. According to one of them, hematopoietic progenitor cells have multilineage potential. The multilineage potential is preserved if the leukemia transformation occurs at this stage. According to the second hypothesis, the lineage switch is caused by the oncogenic reprogramming of the cell [14, 15, 16]. Normal, multipotent hematopoietic stem cells differentiate into myeloid, B or T-lymphoid cells in a complex, gradual maturation process that is influenced by many transcription factors. It depends on their levels, relative time of expression, and mutual interactions, both synergistic and antagonistic [17, 18]. It was shown that B-lineage development is dependent on a high expression of Pax-5 transcription factor, and that the inhibition of Pax-5 by c/EBP alpha induces myeloid or mixed phenotype in common lymphoid progenitor cells [19, 20]. C/EBPalpha is a decisive factor for myeloid differentiation. However, notch signaling is required to promote the proliferation of T-cell progenitors [21].

Diagnostics in MPAL leukemias is challenging. Initially, all leukemias expressing both lymphoid and myeloid markers were called biphenotypic [22]. However, as flow cytometry developed, increasingly more leukemias were shown to express antigens from two different lineages [23]. The first diagnostic criteria of biphenotypic leukemia were gathered in the EGIL classification [3] created in 1995. This classification was based on the immunophenotype. It should be noted that biphenotypic leukemia should not be diagnosed in patients with immunophenotype changes observed during the induction therapy [24, 25]. The second classification is the WHO 2016 classification of myeloid neoplasms and acute leukemias [4]. All acute leukemias of undetermined lineage, that is, leukemias characterized by the presence of more than one cell lineage or the expression of antigens typical for more than one lineage or the absence of antigens characteristic of any lineage, are classified into one group called MPAL. The following subtypes are distinguished: (1) acute undifferentiated leukemia, (2) MPAL with t(9; 22)(q34.1; q11.2); *BCR-ABL1*, (3) MPAL with t(v; 11q23.3); with *KMT2A* rearrangements, (4) B/myeloid MPAL NOS, and (5) T/myeloid MPAL, NOS. It is worth noting that the WHO classification does not only focus on the immunophenotype of blast cells but also highlights the importance of specific genetic aberrations.

The prognosis of MPAL is very unfavorable, as these leukemias are often highly resistant to the therapy. It might be related to a high incidence of specific chromosomal aberrations, including the most commonly described t(9; 22)(q34; q11.2) (Ph chromosome, Ph-positive) and MLL rearrangement [2, 26]. According to the latest reports, mutations associated with adverse prognosis are

often observed in MPAL [5]. Another challenge is the choice of treatment regimen – whether MPAL patients should be treated according to AML, ALL, or a combination protocol [27, 28, 29]. The low number of patients, diagnostic difficulties, and the lack of prospective clinical trials make it difficult to establish uniform, reliable therapeutic protocols. In 2018, Maruffi et al. [30] published the results of a meta-analysis of 1351 patients with MPAL (children and adults). The protocols used in the treatment of ALL and AML as well as "hybrid" regimens (containing drugs used in both) were compared. The incidence of complete remission (CR) was lower in patients treated with AML regiments compared to the group treated with ALL regimens. In addition, in the long-term survival analysis, the efficacy of ALL regimens was at least equivalent to the efficacy of more toxic AML regimens [30]. In patients with MPAL, the early evaluation of the Ph chromosome is important for the treatment decisions [27]. Ph-positive MPAL is usually characterized by a combination of B-lymphocytic and myeloid markers and accounts for approximately 25% of all MPAL cases [31]. Early administration of tyrosine kinase inhibitors is extremely important in this patient population, as it may improve the outcome [32, 33]. Allo-HSCT is indicated in all young patients without significant comorbidities, who achieved CR after induction chemotherapy. In recent retrospective studies, encouraging long-term results of allo-HSCT in MPAL patients in the first complete CR1 remission have been recently shown [34, 35, 36]. In older MPAL patients, hypomethylating drugs appear to be a good alternative, as shown by Lee et al. [37].

There are no standards for the management of patients with acute leukemia with lineage switch or with MPAL. The recommendations published by Gerr et al. [38] suggest that these patients should be treated according to the immunophenotype.

Conclusions

We present two very rare cases of acute leukemia (MPAL and ALL with lineage switch) with unfavorable prognosis in patients previously diagnosed as Ph-negative MPN. Because there is a lack of prospective controlled clinical trials needed to establish treatment standards, we believe that all such cases should be reported. There is a chance that in the future, the development of molecular diagnostics and targeted therapies will improve the treatment outcomes in this population.

Authors' contributions

AO, MS, TW – study design and manuscript preparation. DS – flow cytometry analysis and interpretation, help in preparating the manuscript.

Conflict of interest

The authors declare nothing to disclose.

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None.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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