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Philadelphia chromosome-positive mixed-phenotype acute leukemia: a case report and literature review

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Introduction: Mixed-phenotype acute leukemia (MPAL) is a rare type of acute leukemia with an incidence of less than 5% and Philadelphia chromosome-positive (Ph+) represents a distinct subtype.

Case description: An 18-year-old female complained of recurrent fever with fatigue and chills for one month, and a week of growing lymphadenectasis. Bone marrow examination revealed two distinct populations of blast cells and the presence of *BCR::ABL1* fusion gene, leading to a diagnosis of Ph+ MPAL. The patient received induction chemotherapy of DVAP regimen combined with tyrosine kinase inhibitors (TKIs), and underwent allogeneic hematopoietic stem cell transplantation after achieving complete remission. To date, the patient has maintained sustained hematological and molecular complete remission.

Conclusion: A literature review of 59 cases revealed that Ph+ MPAL is more common in adult, male patients and primarily manifests as B/myeloid subtype. Higher leukocyte counts and chromosome -7 abnormalities have been identified as poor prognostic markers. Acute lymphoblastic leukemia-type therapy is considered more effective for patients with MPAL, and in the TKI era Ph+ has become a subtype with a better prognosis.

KEYWORDS

mixed-phenotype acute leukemia, *BCR::ABL1* fusion gene, tyrosine kinase inhibitor, case report, literature review

Introduction

Mixed-phenotype acute leukemia (MPAL) represents a rare type of acute leukemia with an incidence of less than 5% (1) and has a slight predominance in adult and male patients (2). Characterized by multiple lineage markers on a single blast population (biphenotypic leukemia) or single-lineage markers on distinct blast populations (bilineal leukemia) (3),

MPAL was recognized initially in the 2001 World Health Organization (WHO) classification. Cases of bilineal and biphenotypic leukemia were grouped together and categorized into acute leukemias of ambiguous lineage (ALAL) according to the 2008 WHO classification (4). The diagnosis of MPAL is identified by a number of immunophenotypic markers based on the European Group for the Immunological Characterization of Leukemias (EGIL) or the WHO criteria (Table 1) (5, 6). Two large sample size retrospective studies on MPAL revealed that B/myeloid subtype accounted for 55-59%, followed by T/myeloid (33-35%), B/T (4-12%), and trilineage subtypes (0.9-2%) (7, 8).

The pathogenesis of MPAL remains unclear, and the dysregulation of multiple lineage differentiation due to genetic and epigenetic heterogeneity might play an important role (9). A retrospective study of 39 patients with ALAL revealed that gene mutations were present in approximately 90% of patients, and genes involved in genomic stability and transcriptional regulation were frequently detected in the MPAL cohort (10). Gene mutations identified in MPAL are typically detected in acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) (11, 12). Genomic analysis revealed that *ZNF384* rearrangements were common in B/myeloid-MPAL, whereas biallelic *WT1* alterations were associated with T/myeloid subtype (13). Mutations in the putative chromatin modifier, PHF6, JAK-STAT and Ras signaling pathways are frequently observed in patients with B/T MPAL (14). Moreover, clonal chromosomal abnormalities (CAs) occur in 59%-91% of patients with MPAL (15). As two separate entities of MPAL, *BCR::ABL1* fusion gene induced by t(9;22)(q34.1;q11.2), also known as Philadelphia chromosome-positive (Ph+), was observed in 15%-30% of patients, especially in adults (8); whereas *KMT2A* rearrangement due to t(v;11q23.3) occurred more frequently in the pediatric cohort (16, 17).

Here, we report a case of a young patient with Ph+ MPAL who achieved complete remission (CR) after the first induction therapy involving the combination of tyrosine kinase inhibitors (TKIs) with the ALL-type regimen, and underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) with favorable clinical outcomes. Furthermore, we reviewed the relevant literature to further discuss the clinical characteristics and prognosis of patients with Ph+ MPAL.

Abbreviations: MPAL, mixed phenotype acute leukemia; Ph+, Philadelphia chromosome-positive; TKI, tyrosine kinase inhibitor; WHO, World Health Organization; ALAL, acute leukemias of ambiguous lineage; EGIL, European Group for the Immunological Characterization of Leukemias; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CAs, chromosomal abnormalities; CR, complete remission; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CBC, complete blood count; WBC, white blood cell; LDH, lactate dehydrogenase; ELISA, enzyme-linked immunosorbent assay; VAF, variant allele frequency; CNSL, central nervous system leukemia; DMR, deep molecular response; IS, international scale; CML, chronic myelocytic leukemia; -7, deletion of chromosome 7; OS, overall survival; DFS, disease-free survival; BCP, B-cell precursor; CAR-T, chimeric antigen receptor-T.

Case report

An 18-year-old female patient was admitted to Fujian Medical University Union Hospital in Aug. 2023, who complained of recurrent fever with fatigue and chills for one month, and a week of growing lymphadenectasis. Physical examination showed an anemic appearance, multiple superficial lymphadenectasis and hepatosplenomegaly. The complete blood count (CBC) indicated evident leukocytosis (white blood cell [WBC] counts 127.68×10^9/L), moderate anemia (hemoglobin 69.0 g/L), and normal platelet counts (223×10^9/L). Lactate dehydrogenase (LDH) was markedly elevated at 888 IU/L. Enzyme-linked immunosorbent assay (ELISA) was weakly positive for mycoplasma and influenza B virus IgM antibodies, and a chest CT suggested infection in the middle and lower lobes of the right lung. Peripheral blood smear revealed 22% blasts together with 8.7% eosinophils (Figure 1A). Subsequent BM aspirates confirmed the occurrence of acute leukemia with 25.5% blast cells (Figure 1B), concomitant eosinophilia and secondary myelofibrosis (2+) (Figure 1C). Flow cytometry of the marrow aspirate revealed two populations of blast cells expressing T-lineage (cytoplasmic CD3, CD5, and CD7) or myeloid markers (MPO, CD117, CD33, CD13, and CD15), respectively (Figure 1D). Molecular studies involving gene mutations (Supplementary Table S1) and fusion genes (Supplementary Table S2) for leukemia identified a somatic mutation in *STAG2* (c.459_462 + 10delinsA) with a variant allele frequency (VAF) of 12.4% and *BCR::ABL1* fusion gene (e14a2). Karyotype analysis supported the presence of Ph chromosome (Figure 1E). Based on current evidence, the patient was diagnosed with T/myeloid MPAL with p210-*BCR::ABL1* fusion gene and *STAG2* mutations, then received DVAP regimen (daunorubicin [30 mg/m^2/d ivgtt d1,8,15], vincristine [1.4 mg/m^2/d ivgtt d1,8,15,22], cytarabine [100 mg/m^2 q12h ivgtt d1-7], and prednisone [1 mg/kg/d d1-14, 0.5 mg/kg/d d15-28]) with imatinib (400 mg qd) for induction chemotherapy. The second bone marrow examination in Sep. 2023 revealed morphological CR with only 0.5% blasts, whereas the level of *BCR::ABL1/ABL1* mRNA increased from 64.07% to 88.19% international scale (IS) (Figure 1F), indicating a poor response to imatinib. After the subsequent replacement with dasatinib, the level significantly decreased to 14.84% in Nov. 2023. Considering the young age, sustained CR status, and the presence of adverse genetic abnormalities (*BCR::ABL1* and *STAG2*) for myeloid leukemia (18), the patient received six cycles of intrathecal chemotherapies consisting of methotrexate and cytarabine to prevent central nervous system leukemia (CNSL) and underwent 5/10 HLA-matched haploidentical allo-HSCT from her father in May 2024. The patient achieved deep molecular response (DMR) (*BCR::ABL1/ABL1* mRNA ≤ 0.01% IS (19)) and hematologic CR after transplantation, and has maintained sustained remission to date with regular follow-up.

Literature review

Ph chromosome in adult patients is more common in MPAL than in AML, while the frequency is similar to that in ALL (15, 20).

TABLE 1 Comparison of two primary diagnostic criteria for MPAL.

Markers	EGIL 1995	WHO 2022
Myeloid Lineage		
MPO	2	YES
Lysozyme	2	If MPO-[a]
CD117	1	
CD13	1	
CD33	1	
CD65	1	
CD11c		If MPO-[a]
CD14	0.5	If MPO-[a]
CD15	0.5	
CD64	0.5	If MPO-[a]
Nonspecific Esterase		If MPO-[a]
B-Lineage		
cyCD79a	2	With CD19[b]
cyCD22	2	With CD19[b]
cyIgM	2	
CD19	1	YES
CD20	1	
CD10	1	With CD19[b]
TdT	0.5	
CD24	0.5	
T-Lineage		
CD3 cytoplasmic or surface	2	YES[c] or Immunocytochemistry positive with non-zeta chain reagent
TCR αβ or γδ	2	
CD2	1	
CD5	1	
CD8	1	
CD10	1	
TdT	0.5	
CD7	0.5	
CD1a	0.5	

[a]At least two of these showing monocytic differentiation.
[b]One of these if CD19 strong, at least two if CD19 weak (intensity does not exceed 50% of normal B cell progenitor by flow cytometry).
[c]Intensity in part exceeds 50% of mature T-cells level by flow cytometry.

The presence of p210-*BCR::ABL1* in MPAL should raise suspicion for chronic myelocytic leukemia (CML) in blast crisis, with evidence of prominent splenomegaly and elevated granulocytes in prior history (11, 21, 22). In the present case, the diagnosis of blast phase CML cannot be excluded considering the classic characteristics of significant leukocytosis with eosinophilia, hepatosplenomegaly and secondary myelofibrosis. To clarify the clinical characteristics and prognosis of patients with Ph+ MPAL, we conducted a systemic literature research up to Apr. 2025 on PubMed and Embase databases with keywords and MeSH terms for mixed-phenotype acute leukemia, MPAL, Philadelphia chromosome, and Ph. As summarized in Table 2 including 59 cases (20–36), patients with Ph+ MPAL are considered to have high WBC counts and primarily presented with B/myeloid phenotype (91.30%) (8, 15). There was no significant difference in sex, while a larger proportion of male patients were observed (54.24%) (7, 8, 20, 21). A slight tendency toward the p190 transcript (51.92%) was shown in patients with Ph+ MPAL. Analysis of 21 adult patients revealed no significant difference in clinical characteristics between patients with the p190 transcript and those with the p210 transcript (21). Whether different transcripts are involved in the phenotypic transition of MPAL needs further investigation given their different modes of signaling activation (37). Splenomegaly, hepatomegaly and lymph node enlargement were present in approximately 55.26%, 23.68% and 31.58% of patients, respectively. Additional CAs were shown in nearly 38.78% of cases. Deletion of chromosome 7 (-7), reported in 3/16 cases, appears to be a common CA and is considered an inferior prognostic biomarker, which is mostly a single anomaly in adults but is often accompanied with complex karyotype in children (15). Compared with those with AML or ALL, patients with biphenotypic acute leukemia more commonly present with complex karyotype and extramedullary infiltration (38), while extramedullary infiltration is relatively rare in patients with Ph+ MPAL with only two cases (32, 34). Concomitant *IKZF1* frameshift mutations have been reported in patients with B/M Ph+ MPAL (8), which are more frequent in ALL patients with complex karyotype and associated with a poor prognosis (39).

In general, patients with MPAL are considered to have an inferior prognosis, especially in the older cohort (7, 40). A meta-analysis revealed that ALL-type therapy was statistically associated with a better CR rate and overall survival (OS) than AML-type regimen in the MPAL cohort (41). A multicenter retrospective study indicated that hyper-CVAD therapy (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) showed a significant effectivity and tolerance in patients with ALAL (42). Meanwhile, a study classified MPAL into AML-type and AML-type based on genome-wide methylation signatures, and claimed a better response when giving the lineage-matched therapy (43). B/T-MPAL has been found to share similar genetic characteristics with T-ALL rather than B-ALL, and was defined as a high-risk subgroup of ALL which could also benefit from ALL-based therapy (14). In contrast to subsequent consolidation chemotherapy, early allo-HSCT after initial CR may lead to a better prognosis (44). Prior to the TKI era, patients with Ph+ MPAL were considered to present dismal outcomes without allo-HSCT, especially female patients and those with WBC counts above 100×10^9/L (7, 21). Nevertheless, TKI-combined therapy substantially improved the prognosis of patients with Ph+ MPAL,

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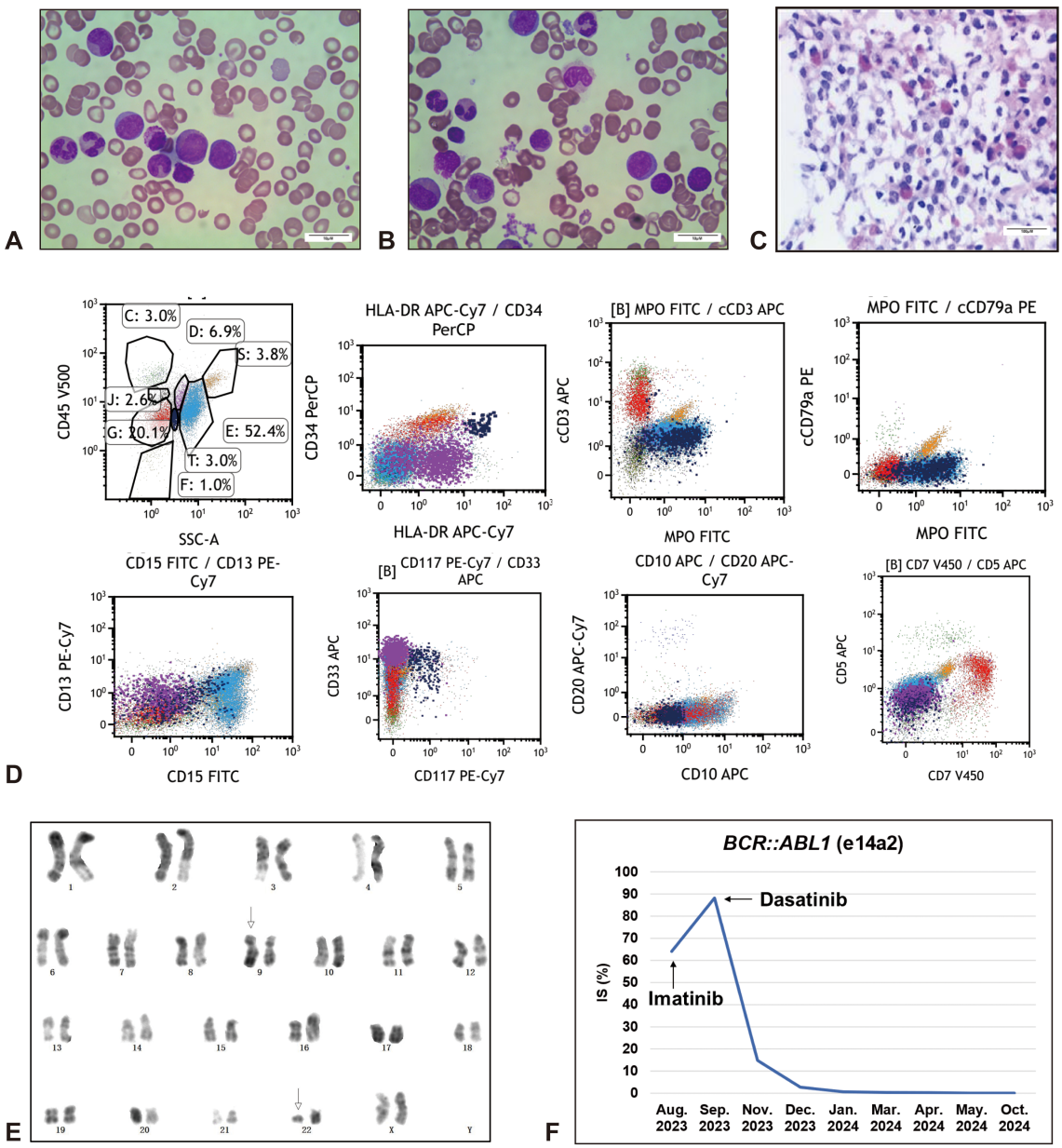

FIGURE 1
Paitent with Ph+ T/M-MPAL. Increased blast cells and eosinophils were evident in the peripheral blood smear **(A)** and bone marrow smear **(B)** (Wirght Giemsa, x1000, scale bar = 10 μm). **(C)** Bone marrow biospy suggested extremely active myeloproliferation (95%), with diffuse infiltration of myeloid blast cells and scattered primitive lymphocytes, marked eosinophilia, and myelofibrosis grade 2 (HE, x100, scale bar = 100 μm). Immunohistochemistry: MPO (+++), CD117 (-), CD34 (+), pax5 (-), CD3 (+), TDT(+), Lysozyme (+++), CD15 (+++), E-Cad (-), GPA (±), LEF1 (±). **(D)** Flow cytometry analysis showed two populations of blast cells by CD45/SSC gating, which were positive for T-lymphoid (cytoplasmic CD3, CD5, and CD7) (red, Group G, 20.1%) or myeloid differentiation (MPO, CD117, CD33, CD13, and CD15) (navy blue, Group T, 3.0%) markers, respectively. Group C, Lymphocytes; Group E, Granulocytes; Group D, Monocytes; Group J, Basophils; Group S, Eosinophils; F, Fragments and other cells. Data were acquired on a BD FACSCanto series flow cytometer (BD Biosciences) and analyzed using Kaluza Analysis software (Beckman Coulter). **(E)** Karyotype analysis by G-banding technique suggested a translocation between chromosome 9 and chromosome 22, t(9;22)(q34;q11), also known as Ph chromosome. **(F)** Dynamic analysis of *BCR::ABL1* fusion gene quantification. IS, International Scale.

which is comparable to those with Ph+ ALL (21, 35, 45). In a small Japanese Ph+ acute leukemia cohort, there were no significant difference in the CR rate, 5-year OS or disease-free survival (DFS) rates between patients with Ph+ MPAL and those with Ph+ B-cell precursor (BCP)-ALL, when matched for influencing factors including age, sex, WBC counts, LDH levels, and the prevalence of additional CAs (35). A cancer registry analysis of 241 patients with MPAL revealed that the Ph+ cohort had a better prognosis than all other subtypes, whereas cases with *MLL* rearrangement were closely associated with poor OS (45). Among the specific cases listed in Table 2, six patients showed no response to TKIs or relapsed after remission. Primary resistance to imatinib was also

TABLE 2 Literature review of patients with Ph+ MPAL.

Ref.	Cases	Subtype	BCR::ABL1 Transcript	Age (yrs)	Sex (M)	WBC (×10^9)	Hemoglobin (mg/dL)	Platelet (×10^9)	Blast% in BM	LDH (IU/L)	Splenomegaly	Hepatomegaly	Lymph Node Enlargement	Additional CA or Karyotype	Mutations	Treatment	Outcomes	Extramedullary Infiltration
(21)	19	B/M	p190 (n=13)	31 (15-42)	7 (53.8%)	41.8 (3.0-681.0)	9.6 (4.5-14.6)	61 (18-150)	NA	NA	8/13	3/13	NA	4/13	NA	1. VDCP ± L-Asp or VDCAP 2. IM (61.9%) 3. allo-HSCT (4/16)	CR: 11/13 2-yrs OS: 23.0% 2-yrs RFS (%): 15.0%	NA
		B/M	p210 (n=6)	30 (18-50)	5 (83.3%)	151.1 (2.6-199.0)	8.8 (6.9-11.7)	69 (12-267)	NA	NA	5/6	1/6	NA	0/6	NA		CR: 4/6 2-yrs OS: 33.0% 2-yr RFS (%) 30.0%	NA
(35)	13	NA	p190 (n=4) p210 (n=9)	52 (16-80)	5 (38.46%)	24.7 (3.3-244.8)	NA	NA	NA	865 (195-1947)	NA	NA	NA	6/13	NA	1. ALL-type (7/13) 2. AML-type (6/13) 3. allo-HSCT (8/13)	CR rates: 100% 5-yr OS: 55% 5-yr DFS: 46%	no
(20)	5	B/M (3/5) T/M (1/5) M/T/B (1/5)	NA	52 (38-61)	4 (80%)	58.6 (18–109)	9.02 (7.2-10.5)	86.2 (60-110)	NA	NA	NA	NA	NA	NA	NA	"7 + 3" regimen (Ara-C+DA)	CR: 2/5 OS: 4 (1-7) months	NA
(33)	4	B/M	p210	3.5	M	19.2	NA	45	NA	NA	mild	mild	yes	NA	NA		CR	NA
		B/M	p190	15	M	72	NA	11	NA	NA	no	no	yes	NA	NA	AML/ALL standard induction protocol+IM	not remission	NA
		B/M	p210	28	M	5.1	NA	381	NA	NA	no	no	no	NA	NA		not follow-up	NA
		B/M	p210	0.58	M	97.4	NA	118	NA	NA	no	no	no	NA	NA		CR	NA
(22)	4	B/M	p210	60	M	41.9	11.2	74.0	68.0	NA	yes	no	no	Complex karyotype without -7	NA	ALL-type+DA	MMR	NA
		B/M	p210	8	F	513.0	5.3	48.0	68.0	NA	yes	yes	yes	46,XX,t (9;22) (q34;q11.2)	NA	NA	NA	NA
		B/M	p210	10	F	376.0	6.7	33.0	48.0	NA	yes	yes	no	46,XX,t (9;22) (q34;q11.2)	NA	AML-type+IM	NA	NA
		B/M	p210	50	F	366.0	8.0	208.0	77.0	NA	yes	no	no	46,XX,t (9;22) (q34;q11.2)	NA	ALL-type+IM	NR	NA
(23)	2	B/M	p210	69	F	33.0	5.9	9.0	88.0	213	no	no	no	46,XX,t (9;22) (q34;q11.2)	NA	Pred+DA	MMR	NA
		B/M (therapy-related)	p190	69	F	160.0	11.3	259.0	99.0	503	no	no	no	46, XX, t (9;22) (q34;q11.2) [14] /46,idem,- 17,+mal [3]/46, XX[3].	NA	Pred+DA	MMR	NA
(24)	1	B/M	p190	85	M	12.9	11.2	70.0	52.0	NA	no	no	no	46, XX, t (9;22) (q34;q11.2)[14]/46, idem,-17,+mal	*TET2*	Decitabine +rituximab-mini-Hyper-CVAD+DA (also as consolidation chemotherapy)	MMR	NA
(25)	1	T/M (therapy-related)	p190	57	F	129	11.6	129.0	40.7	NA	NA	NA	NA	NA	NA	Refused chemotherapy	Death (3 months)	NA

(Continued)

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TABLE 2 Continued

Ref.	Cases	Subtype	BCR::ABL1 Transcript	Age (yrs)	Sex (M)	WBC (×10^9)	Hemoglobin (mg/dL)	Platelet (×10^9)	Blast% in BM	LDH (IU/L)	Splenomegaly	Hepatomegaly	Lymph Node Enlargement	Additional CA or Karyotype	Mutations	Treatment	Outcomes	Extramedullary Infiltration
(26)	1	B/M	NA	61	M	159.5	10.6	35.0	90.0	1607	no	no	no	45,XY,-7, t (9; 22) (q34;q11.2)	*c-MYC*	IM included therapy	Death (1.5 months)	NA
(27)	1	B/M	p190	54	M	49.7	11.8	303.0	70.0	NA	NA	NA	NA	46,XY, t (9; 22) (q34;q11.2)	NA	1st: IDA+CVP+IM 2nd: NI+lenalidomide	CR, Relapse CR	NA
(28)	1	B/M	p190	16	M	12.87	12.0	31.0	89.0	NA	yes	yes	yes	45,XY, dic (7; 9) (p11-13; p13), t (9; 22) (q34;q11) /46,XY	*PAX5::UBE2D4*	DVP+TKI	Relapse, Death (5 months)	NA
(29)	1	B/M	p190	71	F	26.5	10.9	13.3	71.0	1780	no	no	no	45,XX, -7, t (9;22) (q34;q11.2)	NA	IDA+IM/DA/NI (VP as maintenance therapy)	CR, Relapse	NA
(30)	1	B/M	NA	39	F	139.2	10.9	154.0	53.0	NA	no	no	no	46,XX, t (9; 22) (q34;q11.2)	NA	HyperCVAD/ MTX-AraC+IM	NA	NA
(31)	1	B/M	p210	43	F	62.8	6.9	83.0	63.0	NA	no	no	no	46,XX,inv (9) (p12; q13), t (9; 22) (q34;q11.2)	NA	IDA+IM allo-HSCT after CR	Death (10 months)	NA
(32)	1	B/M (therapy-related)	p190	49	F	98.4	10.4	132.0	92.0	NA	NA	NA	NA	Complex karyotype without -7	NA	IDA+IM	MMR	yes
(34)	1	B/M	p190	61	M	150.1	6.7	37.0	diffuse infiltration	785	yes	no	yes	45,XY,-7, t (9;22) (q34;q11.2)[19]/46,XY[1]	NA	Hyper-CVAD+DA allo-HSCT	CR	yes
(36)	1	B/M	p190	87	M	9.9	12.5	20.9	41.0	556	no	no	no	46,XY, t (9; 22) (q34;q11.2)	NA	Pred+DA/low dose-IM	HCR	NA
Present Article	1	T/M	p210	18	F	127.68	69	223	25.0	888	yes	yes	yes	46,XX,t (9;22) (q34;q11.2) [20]	*STAG2*	DVAP+IM/DA allo-HSCT	CR	no

M, male; F, female; VDC (A)P, vincristine+daunorubicin+cyclophosphamide+ (cytarabine)+prednisone; IDA, daunorubicin+cytarabine; Pred, prednisone; AraC, cytarabine; MTX, methotrexate; IM, imatinib; DA, dasatinib; NI, nilotinib; allo-HSCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; NR, not remission; OS, overall survival; RFS, recurrence free survival; DFS, disease free survival; MMR, major molecular response; HCR, hematologic complete remission; NA, not available.

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observed in our present case. It currently unclear whether this is related to myelofibrosis, and further research is needed to explore the superiority of dasatinib over imatinib in such population. In elderly patients with Ph+ MPAL, low-dose TKIs in combination with prednisolone has been identified as a safe and effective therapeutic strategy (23, 36). Moreover, combination therapy with the BCL-2 inhibitor venetoclax is worth trying, as its great advantages in the treatment of elderly patients with AML (46). Given Ph as an adverse prognostic marker in AML, allo-HSCT at an early stage is recommended for eligible patients with myeloid-involved mixed-phenotype leukemia (18, 34). For patients who are not suitable for allo-HSCT, chimeric antigen receptor-T (CAR-T)-cell therapy may be considered as an alternative option in future research (47).

Conclusion

In this study, we report a patient with Ph+ MPAL who received DVAP regimen combined with TKIs, followed by allo-HSCT, ultimately achieving hematologic and molecular CR. Through a literature review, similar to the overall MPAL population, the Ph+ subtype is more commonly observed in adult, male patients, and primarily presents as B/myeloid subtype. As an inferior prognostic marker, high WBC count has also been identified as one of the main characteristics of patients with Ph+ MPAL, while extramedullary infiltration is relatively rare. Chromosome -7 abnormalities have been occasionally reported in patients with Ph+ MPAL and are associated with a poor prognosis. ALL-type therapy is considered to more effective for patients with MPAL. In the TKI era, Ph+ MPAL has gradually become a subtype with a better prognosis. Meanwhile, novel therapeutic strategies are eagerly expected with the emergence of targeted therapeutic agents and immunotherapy.

Author contributions

LY: Formal analysis, Writing – original draft, Visualization, Validation, Conceptualization, Writing – review & editing, Data curation. MH: Data curation, Methodology, Validation, Conceptualization, Writing – original draft, Writing – review & editing. YC: Supervision, Writing – review & editing, Validation, Writing – original draft. YW: Validation, Writing – review & editing, Project administration, Conceptualization, Supervision, Writing – original draft, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2025.1623528/full#supplementary-material

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