CASE REPORT OPEN

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Observation of *PICALM::MLLT10*-rearrangement and coincidental *EZH2* mutations in a patient with acute myeloid leukemia: A case report and review of the literature

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Acute Myeloid Leukemia (AML) with rearranged *PICALM::MLLT10* is a rare and poorly characterized entity. Here, we describe a patient with this rearrangement, and compare this case to the literature. We observed a trend towards young age, male sex, extramedullary involvement (particularly mediastinal myelosarcoma), trisomy 4, trisomy 19 and aberrant CD7-expression. It was suggested that upregulation of *DOT1l* or *BMI1* is a key effector for subsequent leukemogenesis. However, molecular data are not available for most published cases. Interestingly, two different *EZH2*-mutations were detected in our case, while generally being rare in AML, which is concordant with recent reports on the occurrence of *EZH2*mut in this AML subtype. As a synergistic effect of *BMI1* and *EZH2* has already been demonstrated in other neoplasms, we hypothesize that acquiring an *EZH2* mutation might be a crucial proliferation advantage in *PICALM::MLLT10* positive cells. This may explain the high percentage of *EZH2* mutated cases in this entity, but also supports the hypothesis of *BMI1*-mediated leukemogenesis.

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INTRODUCTION

The *PICALM::MLLT10* (also known as *CALM::AF10*) fusion transcript has first been discovered in the U-937 histiocytic lymphoma cell line [1, 2]. It is the product of a translocation of chromosomes 10 and 11 (t(10;11)(p12.3;q14.2)). *MLLT10*-rearranged acute myeloid leukemia (AML) is uncommon. It most frequently occurs as *KMT2A::MLLT10*-fusion, which one study estimates as the third most prevalent KMT2A-rearrangement, being present in 19% of KMT2A-rearranged AML [3]. In comparison, *PICALM::MLLT10* rearranged AML is extremely rare, with the largest published cohort in the adult setting only including 18 cases [4, 5], and the largest pediatric cohort including 39 patients [6]. This is in contrast to MPAL, where the fusion seems more frequent [7], and to gamma-delta-T-cell acute lymphoblastic leukemia (ALL) where the fusion also occurs more frequently [8]. Given its low incidence in AML, the diagnosis can be challenging, as is evident in the case presented here.

It is not entirely clear how *PICALM::MLLT10* leads to leukemogenesis. It has been shown that the interaction of the clathrin-binding-domain of *PICALM* and the OM-LZ region of *MLLT10* is the relevant outcome of the fusion [9]. It has also been shown that several genes, including *BMI1* posterior *HOXA* genes, and *MEIS1* are overexpressed in *PICALM::MLLT10*-positive acute leukemias [10, 11]. However, there are two proposed downstream mechanisms. One focuses on the interaction of a nuclear export signal contained within *PICALM* and the *DOT1L* [9, 12, 13]. This prevents nuclear export of the fusion transcript, and facilitates *PICALM*-dependent upregulation of *HOXA*-family genes (*HOXA 5, 9, 10, MEIS1*), which in turn blocks differentiation of hematopoietic stem cells (HSCs) [14]. The other hypothesis focuses on *BMI1*, which encodes a ring finger protein that is part of the Polycomb Repressive Complex 1 (PRC1). Interestingly, it is not upregulated in *KMT2A*-rearranged AML. The gene is located downstream of *AF10*. PRC1 stabilizes long-term silencing of regions targeted by Polycomb Repressive Complex 2 (PRC2), which represses multiple tumor suppressor genes (e.g., *CDKN2A* and *CDKN2D*). Thus, its upregulation is oncogenic. It has been shown that inhibition of *BMI1* is capable of both inhibiting *PICALM::MLLT10*-driven leukemic transformation and impairing the growth of *PICALM::MLLT10* rearranged AML in several models [15].

We conclude that the case report and literature review presented here will aid clinicians in recognizing this rare entity and understanding its disease biology.

CASE REPORT

A 30-year-old man presented to the Emergency Department of a local hospital 4 times in 11 days with increasing thoracic pain. Due to unspecific ST-elevations on ECG, pericarditis was diagnosed. He was repeatedly discharged with anti-inflammatory and analgesic drugs, until he returned with nausea, myalgias, fever, chills, and sweating. A computed tomography scan was performed (Fig. 1), which revealed a mediastinal mass of 6.5 × 4 × 7 cm, and putative pyelonephritis. The patient was admitted under the suspicion of sepsis. Laboratory studies were compatible with disseminated

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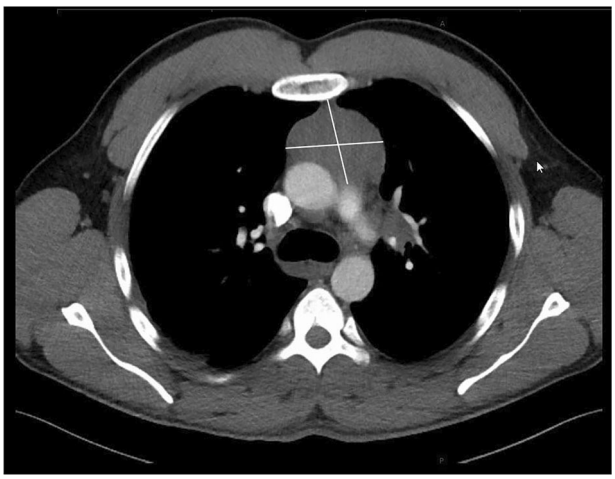

Fig. 1 Axial image from the CT scan taken at diagnosis showing the largest diameter of the mediastinal myelosarcoma.

Table 1. Laboratory studies of the clinical case.

Parameter, Unit	Value	Reference
CBC		
Hemoglobin, g/l	**118**	135–168
Hematocrit, l/l	**0.34**	0.40–0.50
Thrombocytes, G/l	**24**	150–450
Leukocytes, G/l	5.84	3.0–10.5
Blasts, G/l	2.66	0.00
Blasts, %	45.5	0
Neutrophils, G/l	**0.41**	1.60–7.40
Band forms, G/l	**0.09**	0.20–1.40
Eosinophils, G/l	0.06	0.02–0.40
Basophils, G/l	0.00	0.00–0.15
Monocytes, G/l	**0.00**	0.20–0.93
Lymphocytes, G/l	1.49	1.10–3.50
Coagulation Studies		
aPTT, sec.	**49.2**	25.1–36.5
PT, %	**41**	70–120
Fibrinogen, g/l	3.36	2.00–3.93
D-Dimer, µg/l	**>80.000**	<500
Clinical Chemistry		
LDH, U/l	**6553**	125–220
CRP, mg/l	**495**	0–5
CK, U/l	**502**	30–200

Values outside their respective reference ranges are bold.

intravascular coagulation (DIC;Tc: 9 G/l, D-Dimer: >128.000 µg/l, PT: 21 s, Fibrinogen: 2.1 g/l). immune-thrombopenia (ITP) and paraneoplastic DIC were considered, and the patient was transferred to our academic hospital.

At our center, petechiae on abdomen and legs were noted, and the patient reported bleeding easily when brushing his teeth. Neither lymphadenopathy nor organomegalies were present. There was no palpable scrotal mass. An ultrasound of the urogenital tract did not reveal a germ cell tumor. Laboratory studies were notable for massive elevation of acute-phase markers (Table 1).

A blood smear revealed blasts which were morphologically judged to be of primarily lymphatic aspect with immature nucleus and multiple nucleoli. A left-shift of the myeloid lineage was noted. No fragmentocytes were observed. In contrast to the primary cytomorphologic aspect, immunophenotyping of the peripheral blood revealed a large population of myeloblasts (strongly positive for MPO, positive for CD15, CD33, CD34, CD38, CD71, CD105, and CD123), partially positive for CD117, HLA-DR, negative for CD13). A bone marrow biopsy confirmed the diagnosis of AML (FAB M1). The patient received all-trans retinoic acid and arsenic trioxide until *PML::RARα*-rearrangement was ruled out. Cytogenetics revealed t(10;11)(p12.3;q14.2). Interphase fluorescence in-situ hybridization (FISH) and myeloid gene panel (Illumina TSO500 panel) sequencing confirmed a *PICALM::MLLT10* fusion transcript (variant allele frequency (VAF): 38%) and found two mutations in *EZH2* (c.2069 G > A, p.R690H, VAF 36%, ClinVar: likely pathogenic; c.2084 C > T, p.S695L, VAF 36%, ClinVar: pathogenic/likely pathogenic), but no other mutations or rearrangements (65 genes and 688 rearrangements analyzed). Though not definitively deductible from our sequencing data, the presence of two separate *EZH2*mut could hint at a biallelic loss of function. Both *EZH2* mutations we have detected are located in the SET-domain of *EZH2*. According to the Catalog of Somatic Mutations in Cancer (COSMIC) database, one of these mutations (p.S695L) has previously been described in AML, myelodysplastic neoplasm (MDS), ALL, all well as solid tumors, while the other (p.R690H) has been described in a number of hematologic tumors, including AML, MDS, myelofibrosis, Chronic myeloid leukemia, and ALL. Missense mutations in this region abrogate catalytic activity in vitro [16]. Both mutations in the SET-domain as well as homozygous aberrations of *EZH2* show a trend towards worse survival in one large study [17]. Conventional cytogenetics revealed no aberration besides the reciprocal fusion, with t(10;11)(p12.3;q14.2) being detectable in 18/20 metaphases.

The patient then underwent intensive induction chemotherapy with cytarabine and idarubicin ("7 + 3" regimen). Bone marrow biopsy after two cycles showed complete morphological remission, as well as flow-cytometric and molecular measurable residual disease (MRD) negativity, and the remnant of the strongly regressive mediastinal mass was not 18-fluor-desoxy-glucose-avid on positron emission tomography (PET)-CT. We thus considered it most likely that the mass was a myelosarcoma of the present AML and refrained from a biopsy.

The patient then underwent allogeneic stem cell transplant from his matching sister after myeloablative conditioning with cyclophosphamide and busulfan. He received cyclosporine A (CyA) and methotrexate (MTX) as graft versus host disease (GVHD)-prophylaxis. Eleven months after allogeneic stem cell allogeneic transplant, molecular relapse became apparent with an increasing *PICALM::MLLT10* fusion transcript. However, under salvage therapy with azacitidine and venetoclax (aza/ven), the fusion transcript disappeared below the limit of detection (VAF of 2%) again. Unfortunately, seven months after initiation of aza/ven an extramedullary relapse in the form of a progression of the previously described mediastinal mass occurred, while the bone marrow remained MRD negative. Video-assisted thoracoscopic surgery was performed to take a biopsy of the mass, which confirmed the presence of a myelosarcoma, the known *PICALM::MLLT10* fusion and the *EZH2*-mutations. However, in addition mutations in *BRAF* (G469A; VAF 43%), *NRAS* (G12S; VAF 44%) and *TP53* (L145R; VAF 57%) were detected in the mediastinal mass. Activating mutations in *BRAF* are rare in AML and are clearly associated with adverse outcomes [18, 19]. After subsequent radiation of the mediastinal mass (12 × 2 Gray), further extramedullary manifestations of the AML appeared in the patient's pancreas, ribs, and skull. He underwent a second allogeneic stem cell transplant from the same donor (conditioning: Fludarabine and total body irradiation (8 Gray); GVHD-

prophylaxis: CyA, MTX) five months after discontinuation of aza/ven. Subsequently, a maintenance therapy with the BRAF-Inhibitor darafenib and the MEK-Inhibitor trametinib was initiated. This therapy is the standard of care in malignant melanoma with activating *BRAF*-mutations [20]. In AML, *BRAF*-inhibition is not established, but case reports have also shown responses [21]. Unfortunately, the patient did not achieve a long-term remission and died four months after the second transplant.

LITERATURE REVIEW

We searched PubMed for possible spellings of the translocation of interest ("*PICALM-MLLT10*", "*CALM-AF10*", "*PICALM::MLLT10*", "*CALM::AF10*") alone and in combination with "AML" or "Acute myeloid leukemia". Papers including clinical characterizations of patients diagnosed as AML by the respective authors were included. Papers for which no English-language full-text was available were excluded. We identified 118 cases of *PICALM::MLLT10* rearranged AML published in case reports or case series [4, 6, 22–44]. Relevant clinical, immunophenotypic and genetic characteristics of the reported cases are summarized in Table 2. The reported patients are typically younger than the average AML patient with a median age of 14 years at diagnosis (range 6-66). There is a trend towards male sex (71/118). Extramedullary disease is common, with 35 cases reporting some extramedullary involvement. Of these, at least 25 were myelosarcomas (10 mediastinal, 2 abdominal, 1 mammary, 1 uterine, 11 unknown location). However, the type of extramedullary disease was not always specified. Thus, the young, male patient with extensive extramedullary involvement we present here has quite typical clinical features of *PICALM::MLLT10*-rearranged AML.

Karyotypes were available for 63 cases. There was a median of 1 cytogenetic abnormality (range: 0–15) besides *PICALM::MLLT10*. 29 cases had cytogenetic aberrations associated with a poor prognosis, while only one each had an aberration that is associated with favorable/intermediate outcome according to the European Leukemia Net risk stratification from 2022. Eight had trisomy 4 and eight had trisomy 19. In seven patients i17(q10) co-occurred, while no other cytogenetic aberration was co-occurring in more than three cases. Immunophenotypic markers are available for 69 cases. Markers commonly associated with AML were widely reported, while CD7 was the most frequent aberrant marker (27/34 cases). Unfortunately, molecular genetic analyses are not available for the majority of previously reported cases. However, following the introduction of next generation sequencing analysis in increasing numbers of AL patients, newer series make it apparent that *PICALM::MLLT10* has a characteristic comutational profile. The most frequent co-mutations occurred in *PHF6* (22), *TP53* (12), *NF1*, *NRAS*, *SUZ12* (8 each), *WT1* (6) and *EZH2* (5). As our patient also had two EZH2 mutations, we investigated these co-occurrences further. In a series of 15 AL (12 T-ALL, 1 MPAL, 2 AML) patients with *PICALM::MLLT10* rearrangement 4 (including one AML) cases carried mutations in *EZH2*, which usually is very rare in AL, with one report finding one mutation amongst 113 AML cases and another finding no *EZH2*mut in 54 AML patients [16, 29, 45]. Notably, four more patients in the series (including the other reported AML) carried a polymorphism of *EZH2*. Another analysis of *PICALM::MLLT10*-rearranged AL found *EZH2*mut in 6/20 cases (ALAL, T-ALL and AML) [35]. Furthermore, one analysis of *MLLT10*-fusions in pediatric AML found another three patients with the co-occurrence of *PICALM::MLLT10* and *EZH2* mutations [24].

DISCUSSION

The literature to date suggests, that *PICALM::MLLT10* rearranged AML is associated with unusually young age, male sex, and (mediastinal) myelosarcoma, which our case confirms. Unfortunately, our patient seems to confirm the previously reported trend towards adverse outcome. A recent large retrospective analysis

Table 2. Clinical characteristics, karyotypes and immunophenotypes of all adult/adolescent cases with *PICALM::MLLT10* and AML published in the literature.

Parameter	Patients
Male sex	71/118
Age, mean (range)	14 (6–66)
Extramedullary involvement	NA: 17 35/101
Myelosarcoma	25/35 mediastinal: 10 other: 4 localization unknown: 11
Cytogenetic aberrations	available: complete 63[a] partial: 2
Complex or monosomal karyotype	23
+4	8
+19	8
+21	2
Other trisomies ($n = 1$ for all)	8
7	1
−10	2
−17	1
Other monosomies ($n = 1$ for all)	8
t(1;3)(p36;q26)	1
t(1;7)	2
t(9;11)(p31;q15)	1
t(9;22)(q34;q11)	2
Other translocations (ecxl. *PICALM::MLLT10*; $n = 1$ for all)	10
inv(16)(p13q22)	1
add(17)(p11)	1
add(17)(p13)	1
i17(q10)	7
Other structural aberrations	15
Gene Mutations	available: Full molecular genetic report: 35[a] Partial report: 7
ARID1A	1
ASXL1	2
ASXL3	1
CCND3	1
CHD8	1
DPF1	1
EZH2	5
FLT3-TKD	2
JAK21JAK3	3
KMD6A	1
KRAS	3
MYH11	1
NF1	8
NOTCH1	2
NRAS	8
PHF6	22
PTBP1-PALM	1
PTPN11	3
SF3B1	1
SRP72	1

Table 2. continued

Parameter	Patients
SUZ12	8
RUNX1	2
TP53	12
U2AF1	1
WT1	6
Immunophenotype	[a]
CD1	1/7
CD2	2/6
CD3	3/21
CD4	8/19
CD7	27/34
CD8	0/10
CD10	2/9
CD11	12/13
CD13	26/41
CD14	3/12
CD15	6/7
CD19	2/19
CD20	0/5
CD22	0/2
CD25	0/1
CD33	46/53
CD34	29/47
CD38	4/4
CD41a	2/2
CD42	1/6
CD44	1/1
CD45	2/2
CD56	6/9
CD61	3/4
CD64	1/2
CD65	
CD68	1/3
CD71	3/3
CD79a	1/3
CD117	18/35
CD123	3/3
HLA-DR	44/45
MPO	24/42
NSE	1/2
TdT	6/18

[a]For full list of individual patient characteristics see supplementary table 1.

also confirms the negative prognosis in the pediatric population [6]. A large analysis suggests that *MLLT10*, regardless of the fusion partner, always seems to convey adverse outcomes [5].

A significant percentage of published cases (23/63) had a complex karyotype. However, it is unclear whether the genomic instability required to produce these karyotypes is cause or effect of the *PICALM::MLLT10*-rearrangement. While the high incidence of trisomies 4 and 19 that was first noted by Borel et al. [4] is confirmed by other published cases, our patient did not have such aberrations.

As described in the literature, the occurrence of this translocation not only in AML, but as well in both ALL and MPAL points towards its occurrence in a pluripotent progenitor cell compartment [32, 46]. The descendants of this progenitor might then develop into different ALs depending on the differentiation they undergo and secondary alterations accumulated. This could also explain the high latency of AL development in a transgenic murine model [47]. Research in this area is ongoing, with the current WHO classification of myeloid disease hinting at a potential re-definition of *PICALM:: MLLT10* as a MPAL-defining genetic aberration in the next update of the classification [7].

While better genetic characterization of this entity is needed, a pattern of typical co-mutations seems to emerge from our literature analysis. Our case-report matches the published co-mutations well, as the mutations in *EZH2*, *NRAS* and *TP53* all seem frequent in this population. However, NRAS and TP53 are also frequently mutated in other AML [48]. *EZH2* on the other hand seems more closely associated with *PICALM::MLLT10*. *EZH2* is the catalytic subunit of the Polycomb Repressor Complex 2 (*PRC2*), which recruits *PRC1* via methylation markers. Together, they mediate long term epigenetic silencing of chromatin. Studies in hepatocellular carcinoma, esophageal squamous cell carcinoma and prostate cancer have shown a synergistic effect of *BMI1*- and *EZH2*-upregulation, while the interaction in breast cancer seems more complex [49–55]. Therefore, we hypothesize that, if *BMI1*-upregulation is the relevant mechanism of leukemogenesis in *PICALM::MLLT10* positive AL, acquiring an *EZH2* mutation constitutes a crucial survival benefit, leading to selection of *EZH2* mutated clones. This hypothesis would explain the strikingly elevated frequency of *EZH2* mutations in *PICALM::MLLT10* positive AML. Multiple large cohorts of AML patients (Basheer et al.: $n = 2434$; Papapemmanuil et al.: $n = 1540$; Rausch et al.: $n = 1138$; Stasik et al.: $n = 1604$; Wang et al.: $n = 714$), have found *EZH2*mut in 5% (Basheer), 4% (Papaemmanuil, Rausch, Stasik), and 2% of AML cases, respectively, and some smaller studies show barely any cases (1/113, 0/54) [16, 17, 45, 56–59]. *EZH2*mut are associated with worse OS, with one large study observing a trend towards even worse outcomes for homozygous mutations and mutations of the SET-domain [17]. In contrast to the low incidence of *EZH2*mut observed in large unselected cohorts of AML, we and others have shown frequent occurrence of *EZH2*mut in *PICALM::MLLT10* positive AML [24, 29, 35]. However, the potential association between *PICALM::MLLT10* rearrangements and *EZH2*-mut is based on small samples and further studies are needed.

In addition, our hypothesis strengthens the case for *BMI1*-mediated leukemogenesis. Clinically, the possibility of targeting both *BMI1* and *EZH2* therapeutically makes this finding especially relevant [15]. In follicular lymphoma, the *EZH2*-Inhibitor tazemetostat is already approved by the FDA, proving the safety of targeting *EZH2* in humans [60]. In AML *EZH2*-inhibitors have already shown promise in PDX-mouse-models [61].

In conclusion, this report not only highlights and confirms the clinical characteristics of *PICAL::MLLT10*mut AML, but also elucidates key molecular mechanisms as well as potential targets for eventual therapeutic intervention.

DATA AVAILABILITY

As this report contains data of an individual patient, we cannot make the data available to protect our patients privacy.

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AUTHOR CONTRIBUTIONS

CR and TP designed the analysis. UB and JT contributed laboratory and genetic data. MH and KS cared for the patient and contributed clinical data. CR conducted the literature search, analyzed the data and wrote the manuscript. TH and UB contributed to writing the manuscript. All authors edited and approved the manuscript.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE STATEMENT

All methods were performed in accordance with the relevant guidelines and regulations. The study was approved by a decision of the local ethics committee from Berne, Switzerland (decision number #2024-00879; decision date 17.09.2024). Written informed consent as per institutional guideline was obtained from the patient. No identifiable images of the patient are presented in the study.

CONSENT FOR PUBLICATION

The patient described in this report consented to the publication of their case.

ADDITIONAL INFORMATION

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