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Mini Review

Heterogeneous Phenotype of Acute Leukemia with *EWSR1* or *FUS* Gene Rearrangements

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Abstract

Background and objectives: Acute leukemias with chimeric fusion genes involving FET (FUS, EWSR1, and TAF15) family proteins and ETS (E26 transformation-specific)-like transcription factors often present with unique clinical and pathological characteristics. This mini-review aims to summarize the clinical and pathological features of acute leukemia cases harboring rearrangements involving the fused in sarcoma (*FUS*) or Ewing sarcoma breakpoint region 1 (*EWSR1*) genes. ***Methods:*** An extensive literature review was performed on reported acute leukemia cases with fusions involving *FUS* or *EWSR1*. The details of the reported cases, as well as summarized information, are presented. ***Results:*** Rare cases of acute leukemia have been found to harbor either *FUS* or *EWSR1* gene rearrangements with ETS or non-ETS proteins as partners and demonstrate heterogeneous clinical and pathological features. Acute leukemias carrying *FUS* gene rearrangements present with diverse immunophenotypes and are predominantly, but not exclusively, acute myeloid leukemia (AML), with ERG as the most frequent fusion partner. In contrast, acute leukemias with *EWSR1* gene rearrangements more commonly present as B-cell acute lymphoblastic leukemia (ALL) and mixed phenotypic acute leukemia (MPAL), with *ZNF384* as the predominant partner. At present, *FUS::ERG*-positive AML is the only specific entity with a *FET::ETS* fusion that is formally recognized in the World Health Organization 5th edition hematolymphoid tumor classification (WHO-HEM5) and the International Consensus Classification (ICC) systems. Cytogenetic karyotyping and fluorescence *in situ* hybridization remain crucial tools for detecting chromosomal translocations in over half of acute leukemias harboring *FUS* or *EWSR1* gene rearrangements. However, a subset of patients may exhibit a normal karyotype and require advanced molecular diagnostic methods. *EWSR1*-rearranged leukemias can be difficult to distinguish from Ewing sarcoma and therefore require particular attention. ***Conclusions:*** As more cases and additional data become available, it may be justified to expand this category of acute leukemias to include other specific acute leukemia entities with fusions involving FET::ETS, such as *FUS::FLI1* and *FUS::FEV,* in addition to *FUS::ERG*-positive AML. However, additional data are required to support such subclassification. In contrast, AML cases with *EWSR1* rearrangements are exceedingly rare and display considerable variability. Cases of B-ALL or B/myeloid MPAL with the *EWSR1::ZNF384* fusion may be more appropriately classified together with other *ZNF384*-rearranged leukemia subtypes. Advanced molecular diagnostic methods, especially RNA-based next-generation sequencing, are suggested to improve the accurate diagnosis of acute leukemias with *FUS* or *EWSR1* fusions. Additional pathologic workup, particularly immunohistochemical staining with hematopoietic markers, is highly recommended to differentiate *EWSR1*-rearranged leukemia from Ewing sarcoma.

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Introduction

Ewing sarcoma breakpoint region 1 (EWSR1) and fused in sarcoma (FUS), two closely related RNA-binding proteins that belong to the FET (FUS, EWSR1, and TAF15) protein family,[1] are frequently implicated in the chimeric fusion proteins found in a variety of sarcomas. For instance, in Ewing sarcoma, nearly all cases feature rearrangements of ETS (E26 transformation-specific) family genes, with the *EWSR1::FLI1* fusion accounting for approximately 90% of cases and *EWSR1::ERG* for about 5–10%. In most cases, these fusions result in chimeric proteins in which the activation domain from EWSR1 or FUS replaces the N-terminal portion of the ETS protein and fuses with its DNA-binding domain. This structural change leads to aberrant transcriptional activation and enhances the posttranscriptional splicing activity of ETS target genes (Fig. 1).[2] More recently, fusions involving *EWSR1* or *FUS* have been identified in a subset of acute leukemias, displaying diverse clinical and pathological phenotypes, with or without the involvement of ETS-like transcription factors.[3,4] ETS-family transcription factors, which include members encoded by more than 28 distinct genes, are abnormally expressed in a wide range of cancers, such as prostate cancer, tumors of the Ewing sarcoma family, melanoma, secretory breast carcinoma, acute lymphoblastic leukemia (ALL), gastrointestinal

Keywords: Acute leukemia; FET; ETS; EWSR1; FUS; FUS::ERG; EWSR1::ZNF384; Ewing sarcoma.

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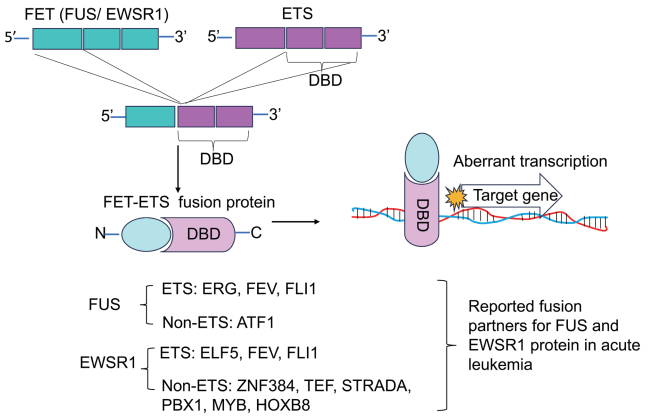

Fig. 1. Schematic representation of the pathogenic mechanism of FET-ETS fusion proteins and reported fusion partners for *FUS* and *EWSR1* in acute leukemia. *FET-ETS* fusions are typically composed of the activation domain from EWS or FUS at the N-terminus fused with the DBD of the ETS protein at the C-terminus. The fusion protein acts as an aberrant transcription factor, leading to aberrant transcriptional activation and enhanced posttranscriptional splicing activity of ETS target genes. Reported fusion partners for *FUS* and *EWSR1* genes in acute leukemia are listed, including ETS and non-ETS proteins. C, C-terminus; DBD, DNA-binding domain; EWSR1, Ewing sarcoma breakpoint region 1; FUS, fused in sarcoma; N, N-terminus.

stromal tumors, and uncommon types of acute myeloid leukemia (AML).[2] Acute leukemias that harbor chimeric fusion genes involving ETS-like transcription factors, such as TEL and ERG, often display unique clinical and pathological characteristics. These features support the need for subclassification of acute leukemias with translocations involving both the FET protein and ETS protein families to enable more precise, targeted treatment strategies.[3,4] In contrast, acute leukemias with fusions involving FET proteins and non-ETS proteins, such as ZNF384, PBX1, and MYB, have also been reported, and their subclassification requires further evaluation. This mini-review aims to summarize the clinical and pathological characteristics of acute leukemia cases involving *EWSR1* or *FUS* gene rearrangements.

Acute leukemia with *FUS::ERG* and other *FUS*-related gene rearrangements

The t(16;21)(p11;q22) translocation is a recurrent chromosomal abnormality found in approximately 0.3–1% of AML cases that are classified among AML with other rare recurring translocations in the recent International Consensus Classification (ICC 2022) and AML with other defined genetic alterations in the World Health Organization 5th edition hematolymphoid tumor classification (WHO-HEM5).[3–5] Early Southern blot and polymerase chain reaction (PCR) studies of bone marrow from a 3-year-old boy with t(16;21)(p11;q22)-positive AML revealed that this translocation results in chimeric proteins typically composed of the N-terminal region of FUS fused to the DNA-binding domain of ERG.[6] Four distinct types of *FUS::ERG* fusion genes have been identified and are classified as A, B, C, and D. These variants produce chimeric transcripts measuring 255, 211, 179, and 349 base pairs (bp), respectively. PCR assays have been developed to detect these transcript isoforms.[7]

Clinically, patients with AML who carry *FUS::ERG* fusions exhibit a wide age distribution but are mainly young adults (median age: 30 years) and tend to present with reduced platelet counts, lower white blood cell counts, occasional eosinophilia, elevated levels of lactate dehydrogenase, and increased bone marrow blasts. Although there is no uniform pattern of differentiation or immunophenotype for these cases, some reports indicate a greater prevalence of the M1 FAB subtype, but this observation is not consistent across all studies.[8,9] Additionally, cases of acute megakaryocytic leukemia (AMKL) and acute basophilic leukemia have been documented in individuals with the *FUS::ERG* fusion gene. The leukemic cells frequently show expression of CD34, CD56, and CD123.[8] Notably, up to 40% of the leukemic blasts demonstrate characteristic cytoplasmic vacuolation or hemophagocytosis.[10,11]

From a genetic standpoint, AML with *FUS::ERG* fusion frequently displays complex karyotypes and trisomy 8, followed by trisomy 10 occurring at a slightly higher rate.[8,9] Mutations in RTK-RAS GTPase pathway genes, including *NRAS* and *PTPN11*, are common, alongside other co-mutations such as *RUNX1*, *DNMT3A*, *ASXL1*, and *BCOR*.[12] Transcriptome studies have shown activation of the phosphatidylinositol-3-kinase-Akt, mitogen-activated protein kinase, and RAS signaling pathways, along with increased expression of BCL2—a target of venetoclax—in *FUS::ERG* AML.[8,13]

Despite recent cytogenetic classifications placing t(16;21)(p11;q22) in the intermediate-risk category, outcomes remain poor.[12] Patients with *FUS::ERG* tend to have a high incidence of relapse.[9] In one study, patients with *FUS::ERG*-positive AML had a median event-free survival of 11.9 months and a median overall survival of 18.2 months. Notably, allogeneic hematopoietic stem cell transplantation did not significantly improve survival.[8] An additional large retrospective analysis demonstrated that survival outcomes following allogeneic hematopoietic stem cell transplantation for AML with t(16;21)(p11;q22) remained poor, irrespective of the risk classification or disease status.[9,14]

Importantly, the *FUS::ERG* fusion is not exclusive to AML. Out of 1,098 pediatric patients diagnosed with B-ALL, four children (0.36%) were identified as carrying the *FUS::ERG* fusion gene.[15] According to reported cases in the literature (Table 1),[15–22] clinical outcomes for patients with *FUS::ERG*-positive B-ALL were variable, and a comprehensive understanding of their clinical, pathological, and genetic characteristics remains incomplete.

Significantly, the FUS gene is capable of creating fusion proteins with the DNA-binding domains of various transcription factors—including ATF1, FEV, and FLI1—in AML as well as other acute leukemias.[5,16,23–25] For example, the *FUS::FEV* fusion gene was also identified in rare cases of T/myeloid mixed phenotypic acute leukemia (MPAL).[24] This raises a key question: Should fusion genes like *FUS::FEV*, *FUS::FLI1*, and similar variants be classified alongside *FUS::ERG*, given their comparable molecular mechanisms and their association with aggressive disease behavior? Recent genetic and RNA sequencing analyses of more than 1,400 pediatric AML cases from Children's Oncology Group trials revealed a wide array of *FUS* fusions, such as *FUS::ERG*, *FUS::FEV*, and *FUS::FLI1*, totaling 25 distinct fusion types.[5,23] Clinical outcomes differed among patients with *FUS* rearrangements.[23] Interestingly, unlike the increased *EZH2* expression seen in *FUS::ERG* pediatric AML, other *FET-ETS* fusion types do not show elevated *EZH2* levels when compared with *FUS::ERG,*[23] suggesting that increased EZH2 is a unique feature of pediatric AML with *FUS::ERG*. Beyond this study, there is a scarcity of data directly comparing the clinical and pathological characteristics of *FUS::ERG*-positive AML with those of other *FET-ETS* fusion subtypes.

Heterogeneous phenotype of acute leukemia with *EWSR1* gene rearrangements

The *EWSR1* gene (22q12.2) is widely recognized for its in-

Table 1. Summary of B-lymphoblastic leukemia cases with *FUS* rearrangements in the literature

Case	Age/sex	Presentation	Diagnosis and phenotype	*FUS*-rearrangement	Therapy and outcome	Reference
1	8-month/ N/A	Anemia, thrombocytopenia, leukocytosis, lymphadenopathy, hepatosplenomegaly	ALL; CD10, CD19, CD20, CD22, HLA-DR, and TdT	45,XY,-16, der(21)t(16;21) (p11.2;q22) [10]/46,XY [10]; FUS (exon 7)::ERG (exon 6)	Induction chemotherapy: relapsed at 4 months follow-up	17
2	1-yr/M	Fever, coughing, anemia, thrombocytopenia, leukocytosis with circulating blasts	ALL; CD10, CD19, CD20, HLA-DR, CD13, CD33	46,XY, t(16;21)(p11;q22); FUS (exon 7)::ERG (exon 6)	Chemotherapy (ALL-oriented protocol to AML -oriented protocol, followed by transplant): In remission at 48 months follow-up	18
3	6-yr/M	Parotid enlargement, cranial nerve VII palsy, hepatomegaly, anemia, circulating blasts	ALL (CD79a, CD22, CD19, CD10, HLA-DR; partially positive for TdT, CD34, CD117)	46,XY,t(16;21) (p11.2;q22) [10]/46,XY [10]; FUS (exon 7)::ERG (exon 6)	Chemotherapy: In remission at 31 months follow-up	19
4	5-yr/M	N/A	B-ALL	46, XY, add(14)(q32), t(16;21) (p11.2;q22)[7]/46,XY[13]; FUS::ERG (by multiplex fluorescence RT-PCR)	In remission at 30 months follow-up	15,16
	3-yr/F	N/A	B-ALL	46, XX [20]; FUS::ERG (by multiplex fluorescence RT-PCR)	In remission at 98 months follow-up	
	4-yr/M	N/A	B-ALL	46, XY [20]; FUS::ERG (by multiplex fluorescence RT-PCR)	In remission at 122 months follow-up	
	4-yr/F	N/A	B-ALL	46, XX [20]; FUS::ERG (by multiplex fluorescence RT-PCR)	In remission at 128 months follow-up	
5	5-yr/F	Anemia, thrombocytopenia, leukocytosis	B-ALL	46,XX,t(16;21)(p11;q22) [5]/46,XX[15]; FUS (exon 7)::ERG (exon 9)	Chemotherapy: In remission at 16 months follow-up	20
6	3-yr/M	N/A	B-ALL	46, XY[20]; FUS::ERG (low level by multiplex fluorescence RT-PCR)	Chemotherapy: Continuous complete remission	21
	4-yr/M	N/A	B-ALL	46, XY, add(11)(p15), add(15) (q22),inc[5]/46, XY[2]; FUS::ERG (low level by multiplex fluorescence RT-PCR)	Haploidentical HCT: Relapsed	
7	4-yr/F	Bruising, splenomegaly, anemia, thrombocytopenia, leukocytosis, markedly increased LDH	B-ALL	46,XX,?t(X;19)(q13;q13.3),der(9); FUS with unknown partner (FISH)	Induction chemotherapy: died of sepsis and cardiopulmonary failure	22

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B-lymphoblastic leukemia or acute B-cell lymphoblastic leukemia; F, female; FISH, fluorescence in situ hybridization; FUS, fused in sarcoma; HCT, hematopoietic stem cell transplantation; LDH, lactate dehydrogenase; M, male; N/A, not available; RT-PCR, reverse transcription polymerase chain reaction; yr, year.

volvement in bone and soft tissue tumors through genetic rearrangements. Nonetheless, recent evidence indicates that *EWSR1* rearrangements can also be found in hematopoietic malignancies, although such occurrences are rare. Unlike AML cases featuring *FUS::ERG* translocations—which are relatively well defined—acute leukemias with *EWSR1* rearrangements display greater heterogeneity and are not currently classified as a distinct entity in the latest hematological guidelines.

As shown in Table 2,[24,26–38] *EWSR1* rearrangements are found in a wide spectrum of acute leukemias. Among these, the *EWSR1::ZNF384* fusion gene stands out as the most common and is predominantly associated with B-ALL and MPAL exhibiting B/myeloid features. The *EWSR1::ZNF384* fusion was initially described by Martini *et al*.,[39] with most cases involving fusion of *EWSR1* to *ZNF384* exon 2 or 3, leaving the *ZNF384* coding sequence intact. In rare cases, the fusion breakpoint in *ZNF384* occurs in exon 7. Mutation and copy number variation data remain limited for *EWSR1::ZNF384* cases, largely because high-throughput sequencing was not available for many earlier reports.[26,27] Nonetheless, fusion genes involving *ZNF384* have been identified in B-ALL, with seven distinct fusion partners reported to date. According to the latest hematopoietic neoplasm classifications, acute leukemia with *ZNF384* rearrangement is now recognized as a distinct disease entity, classified within either B-ALL or MPAL.[4,12] While *ZNF384*-related fusion genes represent a distinct subgroup of B-ALL, the clinical features may still depend on the functional properties of the individual fusion partners.[28]

An *EWSR1::PBX1* in-frame fusion, specifically joining exon 14 of *EWSR1* (NM_005243.3) with exon 5 of *PBX1* (NM_002585.3), has been identified in a B-ALL case with a complex karyotype: 50,XX,+X,t(1;22)(q23;q12),t(2;9)(p13;p22),?inv(13)(q12q34),+14,+18,del(20)(q13.1q13.3),+21[14]/46,XX[6].[29] Notably, the recurrent chromosomal translocation t(1;19)(q23;p13) seen in B-ALL generates the *TCF3 (*formerly known as *E2A)::PBX1* fusion gene, which is found in about 6% of B-ALL cases, predominantly affecting children.[40] The resulting TCF3::PBX1 chimeric proteins act as transcriptional activators, driving cellular transformation. They persistently activate transcription mediated by PBX1 or related PBX family members in leukemic cells by binding to the ATCAATCAA DNA sequence through the PBX1 homeodomain, thereby contributing to the development of leukemia.[41] Historically, this subtype was associated with poor outcomes, but advances in intensive treatment protocols have led to significantly improved prognoses.[4] It is assumed that the functional effects of the *EWSR1::PBX1* fusion closely resemble those seen with *TCF3::PBX1* in B-ALL.[29]

Several case reports highlight the complexity of distinguishing *EWSR1*-rearranged leukemia from Ewing sarcoma. Jakovljevic *et al*. described a 2-year-old girl with a subcutaneous mass who was initially diagnosed with Ewing sarcoma based on a positive *EWSR1* rearrangement and detection of the *EWSR1::FLI1* transcript. However, subsequent identification of lymphoblasts in the peripheral blood, expression of immature B-cell markers, and immunoglobulin heavy chain gene rearrangement prompted a revised diagnosis of B-ALL. The patient responded to chemotherapy and remained in remission.[30] In another example, a 10-year-old patient with a history of B-ALL featuring *ETV6::RUNX1* presented with an atypical malignant shoulder mass. This mass was diagnosed as Ewing sarcoma with an *EWSR1::FLI1* fusion gene but exhibited variable CD43 positivity. It is important to note that CD43 is a hematopoietic marker; its expression typically suggests a non-Ewing sarcoma origin, further complicating the differential diagnosis.[42] In addition, T-cell lymphoblastic leukemia with t(11;22)(q24;q12) and *EWSR1* rearrangement has also been reported.[31]

EWSR1 rearrangements are rarely documented in AML, but an *EWSR1::HOXB8* fusion was reported in a patient with AMKL. Notably, fusions involving HOX cluster genes were present in 14% of AMKL cases in this cohort, and these genetic alterations are known to drive upregulation of HOX cluster gene expression.[32] Other *EWSR1* rearrangements have been identified in AML cases, including *EWSR1::ELF5*, *EWSR1::MYB*, and *EWSR1::FEV*.[24,33] Chromosomal and functional assays demonstrate that the *EWSR1::ELF5* fusion gene promotes oncogenesis by interfering with the p53/p21-dependent pathway.[34] The *EWSR1::MYB* fusion, detected in adenoid cystic carcinoma and various other tumors, leads to increased expression of MYB target genes through the combination of the strong transcriptional activation domain of EWSR1 with the DNA-binding domain of MYB, thereby driving unchecked cell proliferation, enhanced cell survival, and tumor progression.[43] Additionally, a rare case of MPAL with *EWSR1::FEV* fusion was reported in a 41-year-old woman exhibiting immunophenotypic features of B-cell, T-cell, and myeloid lineages. Conventional chromosomal analysis identified a t(2;22)(q35;q12) translocation, and whole-genome sequencing confirmed that this chromosomal rearrangement resulted in the formation of the *EWSR1::FEV* fusion gene.[35] This case underscored the challenges in accurately identifying the translocation partner without advanced sequencing technologies. A third case of B/myeloid MPAL with *EWSR1::FEV* rearrangement was reported by Montgomery-Goecker *et al*.[36,44] Nonetheless, it remains unclear whether *EWSR1::FEV* operates in the same manner as *FUS::FEV*.

Unresolved controversies and future directions

Rare cases of acute leukemia have been found to harbor either *FUS* or *EWSR1* gene rearrangements and to demonstrate heterogeneous clinical presentations, immunophenotypes, and outcomes. The immunophenotypic profiles linked to these uncommon fusion genes are diverse, spanning B-lymphoblastic, T-lymphoblastic, myeloid, and mixed-lineage presentations. Acute leukemias carrying *FUS* gene rearrangements are predominantly, but not exclusively, AML, with *ERG* being the predominant fusion partner. In contrast, acute leukemias with *EWSR1* gene rearrangements more commonly present as B-ALL and MPAL, with rare AML and T-ALL cases reported, and with *ZNF384* as the most frequent partner (Table 3).

A key ongoing question is how to integrate acute leukemia cases with recurring *EWSR1* or *FUS* fusions into future disease classification systems. At present, *FUS::ERG*-positive AML stands as the only *FET::ETS* fusion-specific entity formally recognized in the WHO-HEM5 and ICC classifications, given its unique clinical and pathological characteristics. With the emergence of new cases and data, it may be reasonable to include *FUS::FLI1*- and *FUS::FEV*-positive AML alongside *FUS::ERG*-positive AML. However, additional data are required to demonstrate comparable biological behavior and clinical outcomes among cases with different specific fusion partners. Conversely, *EWSR1*-rearranged AML remains exceedingly rare and demonstrates considerable heterogeneity in immunophenotype, patient age, and clinical outcomes. Although the fusion proteins share common features, in which EWSR1 provides the activation domain while most fusion partners—either ETS or non-ETS proteins—provide the DNA-binding domain, the ultimate biological behavior of acute leukemias is more likely determined by the specific fusion

Table 2. Summary of 18 acute leukemia cases with *EWSR1* rearrangements in the literature

Case	Age/sex	Presentation	Diagnosis (and immunophenotype)	EWSR1-rearrangement	Therapy and outcome	Reference
1	41-yr/F	Pancytopenia	MPAL, B/T/My (CD34+,CD33+,CD19+,CD117+,CD3+, CD7+, MPO subset+, TdT subset+, PAX5 subset+)	t(2;22)(q35;q12); EWSR1::FEV	N/A	35
2	18-yr/M	Skin lesions	B-ALL (CD19+, CD10+,TdT partial+, CD22+, CD79a+, CD20 partial+, Lambda restricted)	t(17;22)(q25;q12); EWSR1::TEF, EWSR1::STRADA	ALL1131 chemotherapy; relapsed and died of disease 6 months later	35
3	2-yr/F	Subcutaneous mass	B-ALL (TdT+, CD19+, CD10+, CD34+, CD99+, FLI1+)	EWSR1::FLI1	Chemotherapy (ALL IC-BFM 2002 protocol); In remission at 30 months follow-up	30
4	35-yr/F	Cytopenia, leukocytosis, lymphadenopathy, splenomegaly	T-ALL (cytoCD3+, CD7+, TdT+, CD99+, surface CD3-)	EWSR1-r+; t(11;22)(q24;q12)	Chemotherapy (ALL protocol); unknown outcome	31
5	10-month/F	Cytopenia, bruising of leg	MPAL, B/My (CD19+, CD79a+,CD38+, CD34+, MPO+, CD117+); a separate B-lymphoblast population	t(2;22)(q35;q12),add(4)(p15.2)[20]; EWSR1::FEV; *STAG2* R529*	Chemotherapy (AML-directed induction; then ALL-directed therapy; followed by transplant); In remission at 46 months follow-up	24,36
6	2-yr/M	Skin lesions	AML (CD34+, CD33+, CD7+, CD61+, CD99+, CD117+)	EWSR1::ELF5	AML directed Chemotherapy followed by transplant; Relapsed 1 yr later and died of disease	34
7	64-yr/M	Anemia, leukocytosis, hepatosplenomegaly	JAK2 V617F positive PMF transformed to AML in 4 months	46,XY,ins(6;22)(q23q11q12),del(22)(q11); EWSR1::MYB	Chemotherapy; unknown outcome	33
8	5-yr/F	Bilateral neck mass, fever, leukocytosis	B-ALL (CD34+, CD19+, CD22+, CD79a+, CD13+, CD33+, CD117+)	46,XX; EWSR1::ZNF384	Chemotherapy followed by transplant; in remission at 13 months follow-up	26
9	4-yr/M	N/A	B-ALL (CD34+, TdT+, CD13+, CD33+, CD15+, CD79a+, cCD22+, sCD22+, CD19+, CD10+)	EWSR1::ZNF384	Chemotherapy, in remission at 32 months follow-up	28
10	29-yr/F	N/A	MPAL, B/My (MPO+, CD34+, HLA-DR+, CD45+, CD33+, CD13+,CD19+, CD22+, CD117−, CD10−)	EWSR1::ZNF384	Relapsed after transplant and died of disease within a month	28
11	N/A	N/A	AMKL	EWSR1::HOXB8	N/A	32
12	Child (unknown age and gender)	N/A	B-ALL	EWSR1::ZNF384	N/A	37
13	Adult (unknown age and gender)	N/A	B-ALL	EWSR1::ZNF384	N/A	37
14	3-yr/F	N/A	B-ALL (CD10-, CD13+, CD33+)	EWSR1::ZNF384	Chemotherapy; In remission at 100 months follow-up	38
15	N/A	N/A	B-ALL	EWSR1::PBX1	N/A	29
16	N/A	N/A	B-ALL	EWSR1::ZNF384	N/A	27
17	N/A	N/A	B-ALL	EWSR1::ZNF384	N/A	27
18	13-yr/F	N/A	AML	EWSR1::FEV	N/A	24

AMKL, acute megakaryoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B-lymphoblastic leukemia or acute B-cell lymphoblastic leukemia; EWSR1, Ewing sarcoma breakpoint region 1; F, female; M, male; MPAL, mixed phenotype acute leukemia; N/A, not available; PMF, primary myelofibrosis; T-ALL, T-lymphoblastic leukemia; yr, year.

Table 3. Summary of acute leukemia with FET family protein fusions

FET family protein	Lineage of acute leukemia	Frequency	Fusion partners (ETS like family and other)	Age range/median age	Male: female	Note on immunophenotype (IP)	Clinical outcome
FUS	AML (predominant M1 FAB subtype)	Predominant	Predominant: ERG; Rare: ATF1, FEV, FLI1	Young adult/30 yr	N/A	AML IP; Frequent expression of CD34, CD56 and CD123; rare AMKL or Acute basophilic leukemia IP	poor with a high incidence of relapse
	B-ALL	Infrequent	ERG	8 month ~6 yr/4 yr	7:3	B-ALL IP; common expression of CD10, CD19, HLA-DR	variable
	T/Myeloid MPAL	Rare	FEV	46 yr	M	N/A	N/A
EWSR1	B-ALL	Predominant	Predominant: ZNF384; Rare: TEF, STRADA, FLI1, PBX1	2 yr~ Adult/4 yr	1:1	B-ALL IP; common expression of CD13 and CD33	variable
	AML	Infrequent	ELF5, MYB, FEV, HOXB8	2 yr~64yr/13 yr	2:1	AML IP with rare AMKL IP	variable
	MPAL	Infrequent	FEV, ZNF384	10 month~41yr/29 yr	F	B/myeloid IP; rare B/T/Myeloid IP	variable
	T-ALL	Rare	N/A	35 yr	F	T-ALL IP	N/A

Among the fusion partners, ETS-like family fusion partners are highlighted in bold font. AMKL, acute megakaryoblastic leukemia; AML, acute myeloid leukemia; B-ALL, B-lymphoblastic leukemia or acute B-cell lymphoblastic leukemia; F, female; M, male; MPAL, mixed phenotype acute leukemia; N/A, not available; T-ALL, T-lymphoblastic leukemia; yr, year.

partners and the subsequent downstream molecular events affecting their target genes. Hence, we suggest that B-ALL or B/myeloid MPAL harboring the *EWSR1::ZNF384* fusion may be more appropriately classified with other *ZNF384*-rearranged acute leukemias, similar to acute leukemia with PBX1 rearrangement.

Cytogenetic karyotyping remains a crucial tool for detecting chromosomal translocations in over half of these cases, with confirmation possible via fluorescence in situ hybridization or other molecular assays. However, a subset of patients may exhibit a normal karyotype, particularly those with B-ALL (Table 1), making the detection of fusion genes such as *FUS::ERG* solely dependent on RNA sequencing or RT-PCR, which presents a significant diagnostic challenge. Therefore, the use of advanced molecular diagnostic methods—especially RNA-based next-generation sequencing (NGS)—holds significant potential for identifying additional cases, enhancing diagnostic precision, improving risk assessment, and facilitating the development of targeted molecular therapies.

Given the reported diagnostic challenges and the clinical significance of distinguishing *EWSR1*-rearranged leukemia from Ewing sarcoma, particular attention should be paid to tissue masses with detection of *EWSR1* and/or *EWSR1::FLI1,* which should prompt further workup to differentiate *EWSR1*-rearranged leukemia (mainly B-ALL, with rare T-ALL or myeloid sarcoma cases) from Ewing sarcoma. Additional immunohistochemical staining with hematopoietic markers, such as CD45, CD43, TdT, PAX5, CD19, CD3, CD1a, MPO, and CD117, supports the diagnosis of lymphoblastic leukemia/lymphoma or myeloid sarcoma and argues against Ewing sarcoma. Staining for CD34 and CD99 is not helpful in this setting, given their possible expression in both leukemias and Ewing sarcoma. In addition, CBC data, flow cytometric analysis of peripheral blood, and B-cell clonality testing can be informative.

Limitations

This mini-review has several limitations. The number of reported cases is relatively small because of the rarity of these entities, which may be partially attributable to the limited routine use of advanced RNA-based NGS in clinical laboratories. Furthermore, detailed information was not always available for all reported cases. Therefore, the summarized data, including the male-to-female ratio, median age, blast immunophenotype, and clinical outcomes, may be biased and less accurate.

Conclusions

Acute leukemias with *FUS::FLI1* and *FUS::FEV* may represent groups related to *FUS::ERG*-positive AML. However, additional data are required to demonstrate shared biological features. *EWSR1*-rearranged AML remains exceedingly rare and highly heterogeneous. Acute leukemias harboring the *EWSR1::ZNF384* fusion may be more appropriately classified with other *ZNF384*-rearranged acute leukemias. Advanced molecular diagnostic methods—especially RNA-based NGS—are recommended to improve the accurate diagnosis of acute leukemias with *FUS* or *EWSR1* fusions. Additional pathological workup is highly recommended to differentiate *EWSR1*-rearranged leukemia from Ewing sarcoma.

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Conflict of interest

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Author contributions

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