DOI: 10.7860/NJLM/2025/80580.2933

Unlocking the Genetic Vault of Acute Myeloid Leukaemia: A Series of Five Cases

M SRIVIDHYA[1], M DOUGUL REGIS[2], K CHANDRAMOULEESWARI[3], UMADEVI SRINIVASAN[4], B MEENAKUMARI[5]

ABSTRACT

Acute Myeloid Leukaemia (AML) is a rare disease in children, accounting for approximately 15-20% of paediatric leukaemic cases. Acute Lymphoblastic Leukaemia (ALL) is the most common cause of paediatric leukaemia with a better prognosis. AML is the leading type of paediatric cancer by its relatively high mortality rate, as it is a genetically heterogeneous, aggressive haematological malignancy. AML results from a series of genetic changes in a haematopoietic precursor cell, altering normal haematopoietic growth and differentiation and leading to the accumulation of large numbers of abnormal, immature myeloid cells in the bone marrow and peripheral blood. Genetic abnormalities play a critical role in leukaemogenesis, influencing disease classification, risk stratification and treatment response. This case series presents five paediatric cases of AML, each with distinct clinical, morphological, immunophenotypic and genetic features. Case 1 was diagnosed as AML M7 with a rare t(1;12)(q21;q24) translocation. Case 2, an infant with AML M4 and CBFB-MYH11 fusion, succumbed to sepsis and refractory shock. Case 3, also AML M4, showed FLT3-TKD and IDH1/2 mutations with intermediate prognosis. Case 4, diagnosed as AML M2/M3 variant, had severe infectious complications but attained Minimal Residual Disease (MRD) negativity. Case 5, an AML M4 with multiple mutations including CBFB-MYH11, NPM1, FLT3, and IDH1/2, also achieved remission. These cases highlight the heterogeneity and complexity of paediatric AML.

Keywords: Cytogenetic abnormalities, Disease stratification, Genetic mutations, Paediatric acute myeloid leukaemia, Prognosis, Therapeutic targets

INTRODUCTION

AML is a disorder of the bone marrow that results from clonal expansion of genetically altered Haematopoietic Stem Cells (HSCs) and haematopoietic progenitor cells, in which acquired genomic aberrations provide a selective growth advantage and impede normal haematopoiesis [1]. Approximately 50% of AML cases have a normal karyotype. AML is reported to have a small number of genetic mutations per case, with over 70 unique driver mutations identified [2]. Acute Megakaryoblastic Leukaemia (AMKL) comprises only about 1% of the adult AML population, whereas in childhood AML its incidence ranges from 4-16% [3]. AMKL is commonly seen in Down Syndrome (DS) children, whereas non DS AMKL and adult AMKL account for less than 1%. AML with inv(16)(p13q22) leads to the CBFB-MYH11 fusion and is usually considered a favourable-risk AML subtype [4]. FLT3 mutations are among the most common genetic alterations in AML, occurring in two major forms: FLT3-ITD and FLT3-TKD. FLT3-ITD has a poorer prognosis than FLT3-TKD [5]. Molecular genetics enhances AML management by enabling precise diagnosis, risk assessment, targeted therapy and relapse monitoring. It continues to drive advancements in personalised medicine, leading to better patient outcomes.

The novelty of these cases is as follows:

Case 1: A rare paediatric AML-M7 case with a novel cytogenetic finding t(1;12) (q21;q24) and absence of RBM15-MKL1 fusion, presenting with a subleukaemic picture and Grade 3 marrow fibrosis.

Case 2: Fatal outcome in infantile AML-M4 with CBFB-MYH11 positivity-highlighting discordance between molecular prognosis and clinical severity.

Case 3: Paediatric AML-M4 with rare co-occurrence of FLT3-TKD and both IDH1/2 mutations-clinical and prognostic implications in the evolving molecular era.

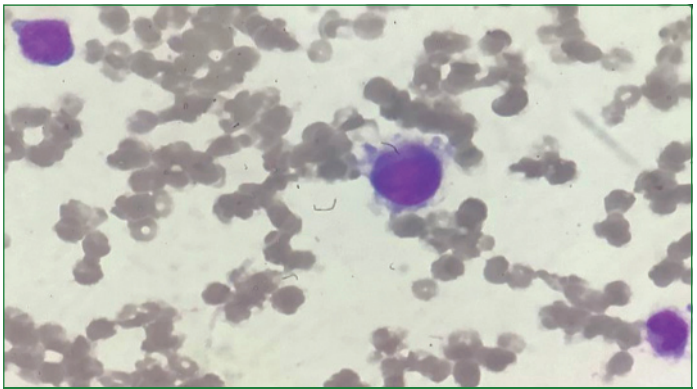
Case 4: A case of AML M2/M3 variant with aberrant CD7 positivity and no fusion gene-importance of immunophenotyping in lineage ambiguity and MRD-guided therapy.

Case 5: Paediatric AML with co-occurring CBFB-MYH11, FLT3-TKD, NPM1 and IDH mutations- a rare genomic constellation with good response to induction chemotherapy.

CASE SERIES

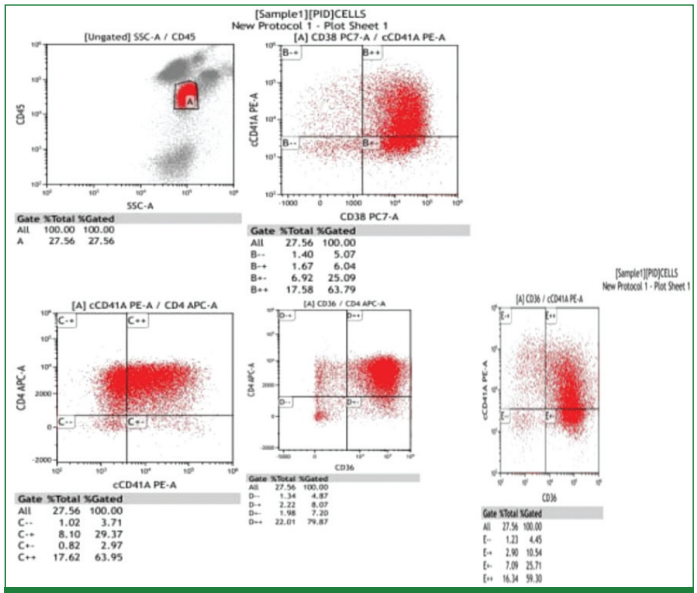
Case 1

A two-and-a-half-year-old, second-born male child presented with fever for six days, along with cough and cold for one week. There was no family history noted. He was admitted and evaluated. Complete blood count revealed bicytopenia (RBC 2.23 x 10^12/L) and platelets 26,000/µL. Ultrasound showed hepatomegaly and splenomegaly with minimal ascites. Peripheral smear revealed a subleukaemic picture with blasts at 16%. He was initially started on antibiotics and antipyretics. Other investigations, including Renal Function Tests (RFT), Liver Function Tests (LFT), urine routine and urine culture, were normal. He was referred to haematology; bone marrow aspiration and biopsy both showed acute leukaemia with blasts 22% [Table/Fig-1] and Grade 3 marrow fibrosis. The blasts were large, with an increased nuclear-to-cytoplasmic ratio, deep

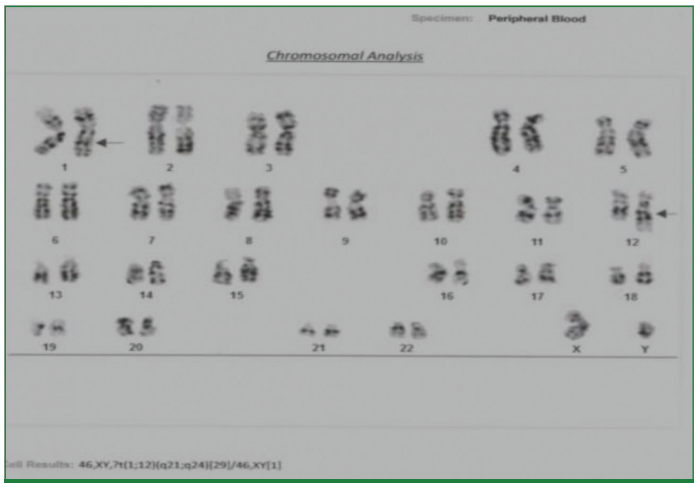


[Table/Fig-1]: Photomicrograph of blast with increased nuclear cytoplasmic ratio with stippled chromatin having cytoplasmic blebs and some showing cytoplasmic vacuoles (H&E, 100x magnification).

blue agranular cytoplasm and fine chromatin with 2-3 inconspicuous nucleoli. Flow cytometry of the bone marrow showed parameters and antigen expression favouring AMKL, with blasts 26% expressing dim CD45, CD41, CD36, CD38, CD33 and aberrant expression of CD4 and CD56 [Table/Fig-2]. Mutational studies by Polymerase Chain Reaction (PCR) ruled out RBM15-MKL1 fusion associated with AMKL. Karyotyping revealed a rare translocation: 46,XY, t(1;12)(q21;q24) [Table/Fig-3]. Hence, the final diagnosis was AMKL-AML M7 with blasts 26%. He was started on cytarabine and daunorubicin (3+7) induction. One unit of blood and two units of platelets were transfused. Bone marrow assessment after induction showed remission (<5% blasts).



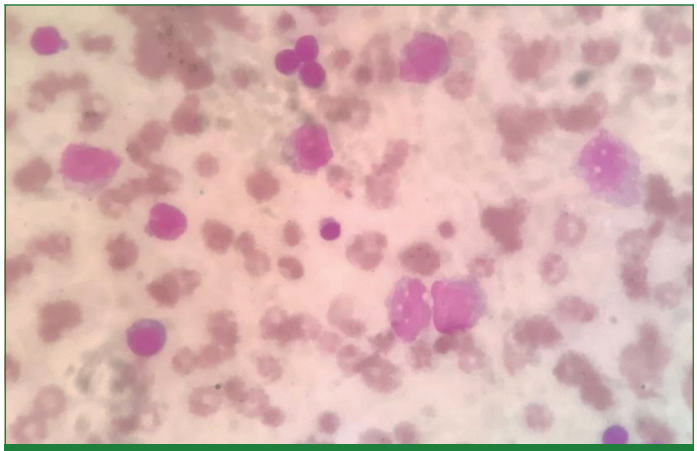
[Table/Fig-2]: Flowcytometry showing CD41 and CD36 exhibiting moderate positivity.



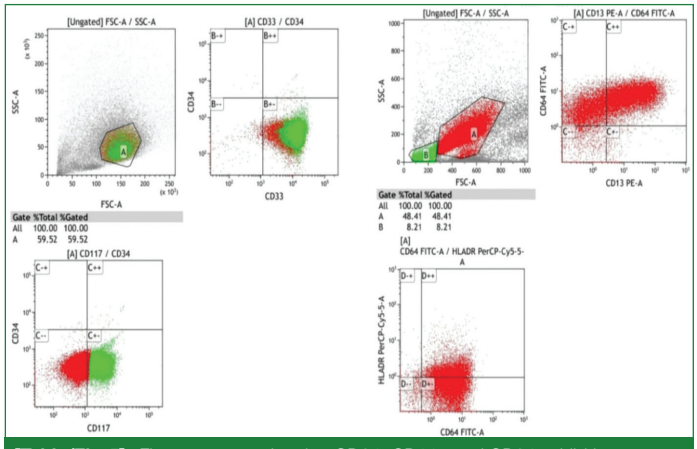
[Table/Fig-3]: Karyotyping showing chromosomal translocation of 46XY,t (1:12) (q21;24).

Case 2

An 11-month-old, first-born female child presented with cough and cold for one month. On examination there was bilateral cervical lymphadenopathy and hepatomegaly. There was no supportive family history. She was admitted and evaluated. Complete blood count showed marked leukocytosis (WBC 52,600/µL). Peripheral smear showed dimorphic anaemia (normocytic normochromic with macrocytosis) with thrombocytopenia and leukocytosis, with 15% blast cells admixed with atypical/monocytoid cells (36%) [Table/Fig-4]. Ultrasound showed hepatomegaly and Grade I Renal Parenchymal Disease (RPD). Echocardiography showed pericardial effusion. Flow cytometry of blood, in correlation with peripheral smear, showed blasts 15% and promonocytes 45% (blast-equivalent), favouring acute leukaemia. CD45 was dim positive (21%), monocyte region 54% in the low side scatter gate, MPO dim positive, moderate positivity for CD64, CD4, variable positivity for HLA-DR, bright positivity for CD33, CD13, CD14. CD34 and CD117 co-expression of 17%, with positive expression of CD56 and CD123 [Table/Fig-5]. PCR showed CBFB-MYH11 positivity. She was started on allopurinol and rasburicase, with a unit of blood transfusion. The child developed persistent fever spikes with tachycardia, tachypnoea, and decreased oxygen saturation; thus she was started on high-end antibiotics (meropenem) and admitted to Intensive Care Unit (ICU) on high-flow nasal cannula. Echocardiography showed Grade I left ventricular diastolic dysfunction with an ejection fraction of 50%. After stabilisation, she was started on a 3+7 AML induction therapy with daunorubicin, rasburicase and spironolactone. She subsequently developed respiratory distress, facial puffiness, abdominal distension and fever spikes; in view of desaturation, she was intubated and started on an inotrope (adrenaline) for septic shock. Blood pressure remained low despite treatment. Glasgow Coma Scale was E1T1M2, with bilateral non reactive pupils. There was a sudden onset of bradycardia with oxygen saturation of 52%; cardiopulmonary resuscitation was performed. Despite resuscitative measures, the child could not be revived and died with the cause of death attributed to AML M4/ sepsis/pericardial effusion/refractory shock. CBFB-MYH11 positivity is usually associated with a favourable prognosis; however, in this case the prognosis was poor.



[Table/Fig-4]: Photomicrograph of blast which are large cells with increased nuclear cytoplasmic ratio, round nucleus stippled chromatin and 2 to 3 conspicuous nucleoli with moderate cytoplasm (H&E, 100x magnification).

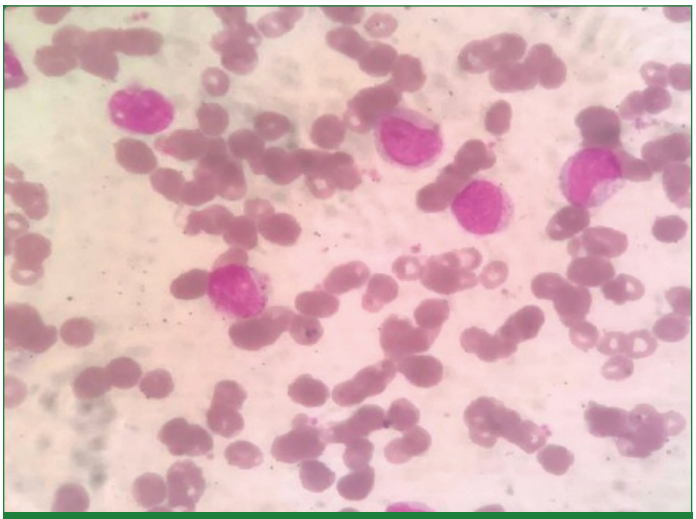


[Table/Fig-5]: Flowcytometry showing CD64, CD117 and CD34 exhibiting moderate positivity.

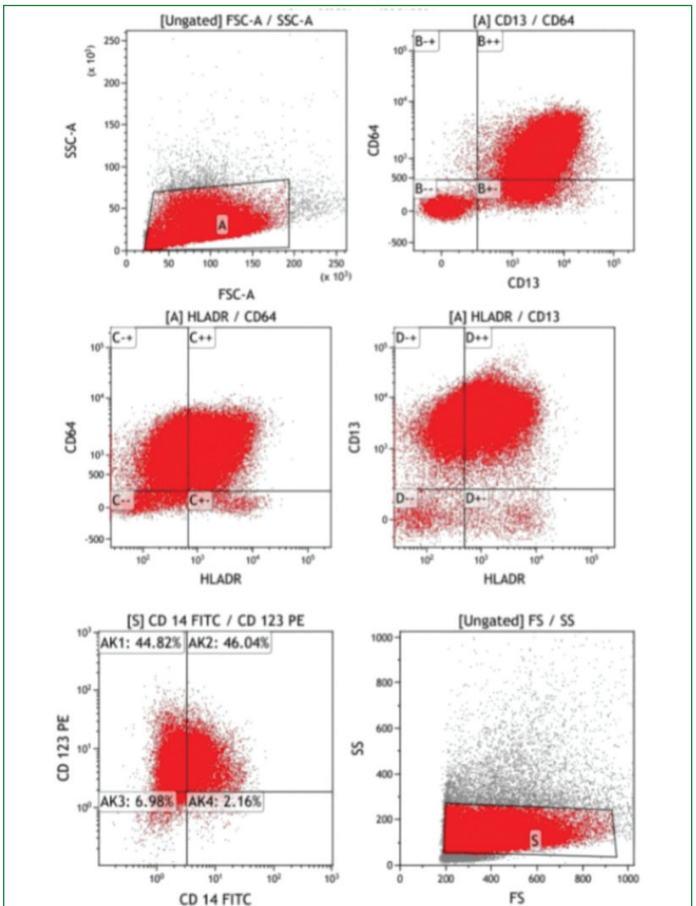
Case 3

A one year seven months old male child presented with fever for one week and abdominal distension and no other complaints. On examination, the liver was palpable. Complete blood count and peripheral smear showed bicytopenia (Hb 7.5 g/dL, platelets 78,000/µL) and atypical cells suggestive of acute leukaemia [Table/Fig-6]. Flow cytometry showed expression of myelomonocytic markers: CD33 dim positive, CD117 moderately positive and

cytoplasmic MPO moderate positive; Stem cell markers CD34 and HLA-DR moderately positive and CD123 dim positive. In addition to the blasts, the monocyte population constituted 20.2%, expressing moderate CD64, CD36, bright CD33 and dim CD15 positivity [Table/Fig-7]. These features are suggestive of Acute Myelomonocytic Leukaemia (AML-M4). Admitted for evaluation and treatment. Molecular studies were positive for FLT3 TKD (D835Y, D835V, D835H) and IDH1 R132 mutation and IDH2 R140 mutation. Karyotyping was normal. The patient was started on (3+7) AML induction therapy with daunorubicin and cytarabine. The child developed loose stools and fever with melena during therapy and was treated accordingly. After the first cycle there was severe leucopenia with thrombocytopenia. Bone marrow showed normocellular marrow with blasts 5%. FLT3 TKD and IDH mutations usually have a good prognosis, but in this patient the prognosis was intermediate.



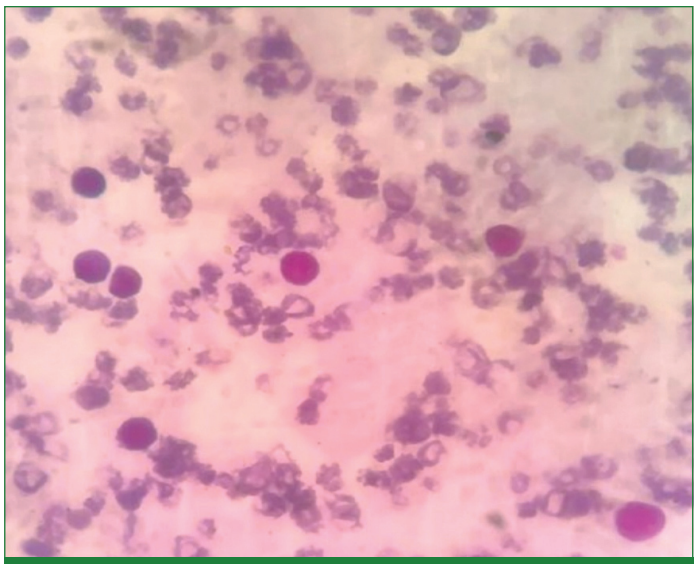
[Table/Fig-6]: Photomicrograph atypical cells in peripheral smear (H&E, 100x magnification).



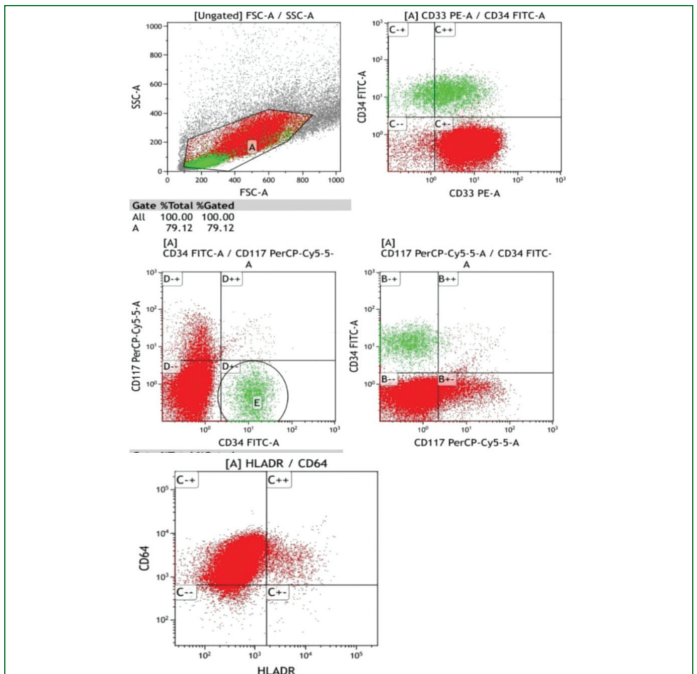
[Table/Fig-7]: Flowcytometry showing CD64 and HLADR exhibiting moderate positivity.

Case 4

A 12-year-old female presented with fever for five days. Complete blood count revealed elevated total leukocyte count (WBC 55,600). On examination, splenomegaly was present. Peripheral smear showed acute leukaemia with blasts 63%; bone marrow aspiration showed blasts 62% [Table/Fig-8]. Flow cytometric analysis showed a cluster in the CD45 dim region with low side scatter. Gated events in the blasts (80% of acquired events) showed moderate expression of CD33, HLA-DR, CD7, dim expression of CD13, CD34, CD45, CD117, partial dim expression of MPO, and the rest of the markers were negative [Table/Fig-9]. The scatter parameters and antigen expression profile studied by flow cytometry were suggestive of AML M2/M3V. Karyotyping was normal. FLT3 mutation, PML-RARA fusion, AML1-ETO fusion and CBFB gene rearrangements were not identified. The patient was started on induction AML therapy with daunorubicin and cytarabine (3+7) but was stopped on day 5 due to complications such as cardiotoxicity, septic shock and fungal pneumonia; she was started on spironolactone and voriconazole and was also started on (3+2) ALL induction with cytarabine and mitoxantrone. After the first induction, flow cytometry for MRD showed no MRD detected; AML MRD was <0.1%.



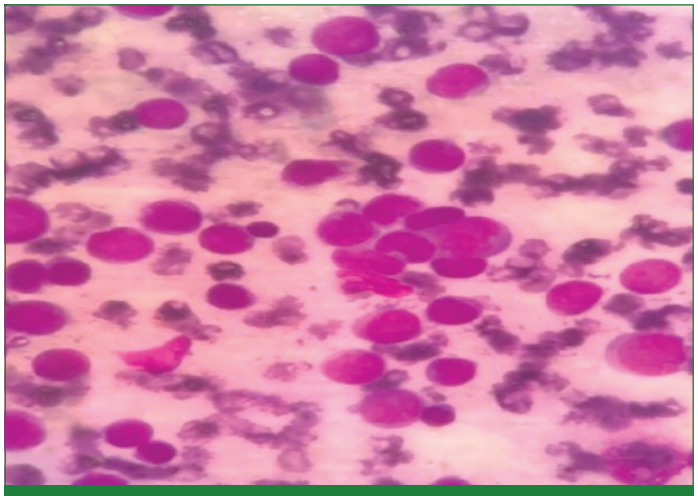
[Table/Fig-8]: Photomicrograph of acute leukaemia with blast 62% in bone marrow aspiration (H&E, 100x magnification).



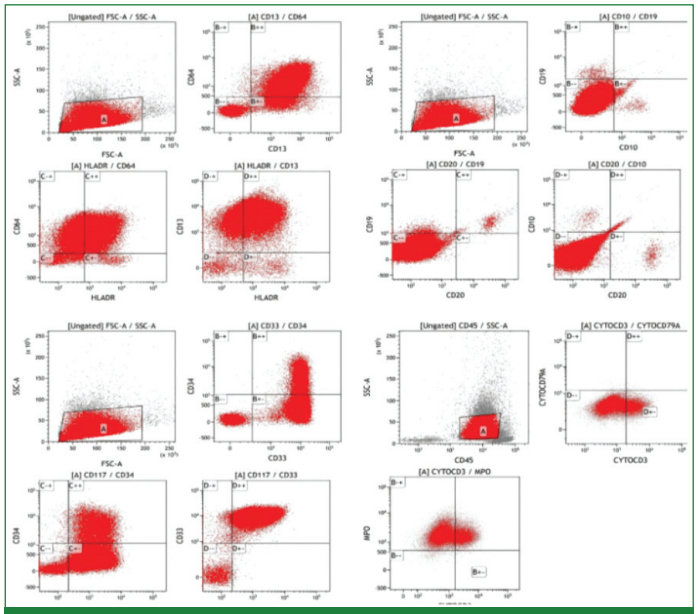
[Table/Fig-9]: Flowcytometry showing CD33, CD117 and HLADR exhibiting moderate positivity.

Case 5

An 11-year-old female presented with fever for one week and hepatosplenomegaly. She was admitted for further evaluation and management. Peripheral smear showed normocytic, normochromic anaemia with leukopenia and thrombocytopenia. Bone marrow aspiration revealed markedly hypocellular marrow with blast cells comprising 4% [Table/Fig-10]. Flow cytometry showed a cell cluster in the CD45 dim to moderate region with low to moderate side scatter. These gated cells demonstrated bright CD33 expression, with moderate positivity for CD117, CD13, CD34, and CD64; dim positivity for MPO and HLA-DR; and negative expression of CD19, CD10, CD20, cytoplasmic CD79a, CD3, CD7, and cytoplasmic CD3 [Table/Fig-11]. The scatter parameters and antigen-expression profile observed by flow cytometry of the peripheral blood sample were consistent with AML-M4 (myelomonocytic leukaemia), with 50% blasts. Molecular studies were positive for CBFB-MMYH11 translocation. NPM1 mutations were detected (types A, B, and D; duplication of nucleotides 956–959). A FLT3-TKD mutation at codon 835 (and 836) and IDH1 R132 and IDH2 R140 mutations were also identified. The patient has a rare combination of FLT3-TKD mutation co-existing with CBFB-MYH11 rearrangement. The patient was started on induction AML therapy with daunorubicin and cytarabine (3+7). After induction, the marrow showed normocellular marrow with mild erythroid hyperplasia and blast percentage within the normal range, indicating remission and a good prognosis. All cases discussed above are summarised in [Table/Fig-12].



[Table/Fig-10]: Photomicrograph of markedly diluted marrow with blast 4% (H&E, 100x magnification).



[Table/Fig-11]: Flowcytometry showing CD34, CD64 and MPO exhibiting moderate positivity.

DISCUSSION

The AML is the major form of leukaemia in newborns and adults, but during infancy and adolescence it represents a smaller fraction, constituting approximately 15-20% of all paediatric leukaemia cases, while in adults it accounts for about 80% of acute leukaemias [1]. The exact incidence rate of paediatric AML in India is not well documented, primarily due to underreporting and underdiagnosis. However, based on global data, the incidence of AML in children is estimated to be around six cases per million per year. Due to the development of various optimised therapeutic regimens and allogeneic stem-cell transplantation, the overall survival rate of childhood AML has approached 70%, but it remains lower than that for paediatric ALL [6]. Peripheral smear and bone marrow examination are performed when leukemia is suspected, and the percentage of blasts is assessed. Immunophenotyping is performed by flow cytometry; based on the lineage of the leukaemic cells, cytogenetic and molecular analyses are performed using karyotyping and PCR.

The classification of AML has evolved to emphasise major advances in recent years, foremost being the separation of AML with defining genetic abnormalities from AML defined by differentiation [7]. The historical requirement of 20% blasts for AML types with defining genetic abnormalities has been eliminated. AML with BCR-ABL1 and AML with CEBPA mutations are the only disease types with defined genetic abnormalities that historically required at least 20% blasts for diagnosis [2]. AML with rearrangements involving KMT2A, MECOM and NUP98 can have fewer than 20% blasts and still be clinically similar to high-blast AML [6]. A third development is the introduction of a section on AML with other defined genetic alterations, providing a landing spot for new or uncommon AML subtypes.

Genes affected by somatic mutations in AML are diverse, but a few recurrent somatic mutations occur in more than 5% of cases: FLT3, NPM1, WT1, CEBPA and KIT. This is in contrast with adult AML, where alterations in TP53, DNMT3A, IDH1 and IDH2 are common; the same are rare in children. In contrast to somatic sequence variants, paediatric AML has a higher rate of chromosomal rearrangements, with rearrangements involving RUNX1, CBFB and KMT2A occurring in more than 35% of childhood AML [6]. Copy-number variants are relatively infrequent in most paediatric AML, but AMKL exhibits a higher rate of copy-number alterations than other pediatric AML subtypes.

Based on the cytogenetic profile and the heterogeneous nature of the disease, AML patients can be stratified into favourable, intermediate and adverse risk groups. Major recurrent cytogenetic abnormalities in AML, such as t(8;21)(q22;q22), t(15;17)(q22;q12), and inv(16)(p13q22)/t(16;16)(p13;q22), emerge as markers for favourable outcomes with longer remission and survival [6]. Monosomies of chromosomes 5 or 7, deletion of the long arm of chromosome 5, and abnormalities of the long arm of chromosome 3, such as inv(3)(q21q26) and t(3;3)(q21;q26), or a complex karyotype, are associated with poor prognosis and increased risk of relapse [1].

The FLT3 gene is one of the most recurrent somatic mutations in AML, located on chromosome 13q12 and encodes a membrane-bound Receptor Tyrosine Kinase (RTK) that belongs to the RTK class III family [1]. There are two major types of FLT3 mutations: ITD mutations in the juxtamembrane domain (FLT3-ITD) and point mutations or deletions in the tyrosine kinase domain (FLT3-TKD). Both mutant FLT3 molecules are activated through ligand-independent dimerisation and transphosphorylation [7]. The most common activating FLT3 mutation is FLT3-ITD, observed in 10-15% of pediatric cases. The prognosis of AML with FLT3-ITD depends on cooperating mutations; NPM1 co-mutations are associated with the best prognosis, whereas the presence of WT1 mutations or NUP98-NSD1 fusions is associated with a worse prognosis compared with FLT3-ITD alone. FLT3-TKD mutations generally have a slightly less negative impact on survival compared to ITD

Case	Age and gender	Chief complaints	Imaging	Peripheral smear	Bone marrow findings	Flow cytometry	Molecular studies	Treatment	Prognosis
1.	2½ years M	Fever, cough	Hepatomegaly, splenomegaly	Sub leukaemic Blood picture with blast 16%	Acute Leukaemia with blast 22% and Grade 3 marrow fibrosis	Blast cells 26%, expressing dim CD45, CD41, CD36, CD38, CD33 and aberrant expression of CD4 and CD56 favouring Acute Megakaryoblastic Leukaemia (AMKL)	PCR: RBM15-MKL1 mutation negative. Karyotyping -translocation of 46XY,t(1;12)(q21;24)	Inj. Cytrabine and Inj. Daunorubicin in a (3+7) Induction	Good prognosis
2.	11 months F	Cough, cold, lymphadenopathy	Hepatomegaly	Dimorphic anaemia with thrombocytopenia and leukocytosis with 15% blast cells admixed with atypical cells/ monocytoid cells (36%)	Not done	Blast count 15% and Promonocyte 45% (blast equivalent) favours Acute Leukaemia. CD 45 dim positive (21%), monocyte region 54% in low side scatter, MPO dim positive, moderate positive for CD64, CD4, variable positive of HLA-DR, bright positive for CD33, CD13, CD14. CD34 and CD117 markers co-expression of 17%, positive expression of CD56 and CD123.	PCR: CBFB-MYH11 positive	Inj. Daunorubin, Inj. Rasburicase in a (3+7) Induction	Died on 5th day of diagnosis
3.	1 year 7 months M	Fever, abdominal distension	Hepatomegaly	Atypical cells suggestive of acute leukaemia	Not done	Expression of myelomonocytic markers like CD33 dim positive, CD 117 moderate positive and cytoMPO moderate positive, stem cell markers like CD34 and HLA-DR moderate positive and CD123 dim positive. In addition to the blasts, the monocyte population constitute 20.2% expressing moderate CD64, CD36, bright CD33 and Dim CD15 positivity. Acute Myeloid Leukaemia- M4.	PCR: positive for FLT3 (TKD-D835Y, D835V, D835H), IDH1 – Amino acid arginine Codon 132 Mutation and IDH2 Amino acid arginine Codon 140 Gene Mutation. Karyotyping - Normal	Inj. Daunorubicin and Inj. Cytarabine in a (3+7) Induction	Poor prognosis
4.	12 years F	Fever	Splenomegaly	Acute leukaemia with blast 63%	Acute leukaemia with blast 62%	Cluster in CD45 dim region with low side scatter. Gated events in blasts (80% of acquired events) region shows moderate expression of CD33, HLA-DR, CD7, dim expression of CD13, CD34, CD45, CD117, partial dim expression of MPO and rest of the markers are negative. The scatter parameters and Antigen expression profile as studied by the flowcytometry of the sample are suggestive of AML M2/M3V.	Karyotyping was normal. Mutation of FLT3 gene, PML/RARA fusion, AML1/ ETO fusion, CBFB gene was not identified.	Inj. Daunorubicin and Inj. Cytarabine in (3+7) AML Induction but stopped on day 5 due to development of complications such as cardiotoxicity, septic shock and fungal pneumonia and started on Spironolactone and Voriconazole. Later was started on (3+2) ALL Induction of Inj. Cytarabine and Inj. Mitoxantrone.	Good prognosis
5.	11 years F	Fever	Hepatosplenomegaly	Normocytic normochromic anemia with leucopenia with thrombocytopenia.	Markedly diluted marrow with peripheral blood with blast 4%	Cell cluster in CD45 dim to moderate positive region with low to moderate side scatter. These gated cells show bright positive expression of CD33, moderate positive expression of CD117, CD13, CD34, CD64, Dim positive expression of MPO, HLADR, Negative expression of CD19, CD10, CD20, CYTOCD79a, CD3, CD7, CYTOCD3. The scatter parameters and antigen expression profile as studied by flow cytometry of the peripheral blood sample shows AML- Myelomonocytic Leukaemia with blast 50%.	PCR –co-existing positive for CBFB-MYH11 Gene Translocation. Positive for Gene Mutation: NPM1(type -A, B, D (Duplication of Nucleotide position 956-959), FLT3-TKD1 -CODON 835 and 836, IDH 1 - CODON 132, IDH2 – CODON 1400.	Inj. Daunorubicin and Inj. Cytarabine in (3+7)AML Induction	Good prognosis

[Table/Fig-12]: Summary of the clinical features and investigations of the presented cases.

mutations. Having both FLT3-TKD and IDH mutations together can be associated with a poorer prognosis compared with having only one of these mutations [8]. However, FLT3-TKD with inv(16) has a comparatively better prognosis than FLT3-TKD alone.

Several molecular mutations can give rise to AMKL, which arises mainly in three clinical groups: children with Down syndrome, children without Down syndrome, and adults [9]. Immunophenotyping and detection of markers of megakaryocytic differentiation play an important role in the diagnosis of AMKL and in the diagnosis of the newly termed "RAM immunophenotype," which correlates with CBFA2T3::GLIS2, a subtype of AML with other defined genetic alterations [10]. The translocation 46,XY, t(1;12)(q21;q24) is very rare and is associated with AMKL; its prognosis is not known due to its rarity.

Inv(16)(p13q22) is associated with the AML M4 subtype, which is characterised by the presence of myelomonocytic blasts and abnormal eosinophils. This chromosomal rearrangement results in the fusion of CBFB and MYH11 genes [11,12]. More than 10 CBFB-MYH11 fusion transcript variants have been reported, of which type A is present in about 85% of patients with inv(16)/t(16;16). It is believed that all patients with a CBFB-MYH11 fusion have a favorable clinical course, regardless of the fusion variant [13], but in this case (Case 2) there was a worse prognosis.

RUNX1 is one of the most frequent mutations in newly diagnosed AML patients, with a frequency of 6–15% in adults and less common in childhood [14]. Most studies have shown that RUNX1-mutant status is associated with adverse clinicopathological features and poor prognosis. Somatic mutations in the NPM1 gene are found in 2-8% of the paediatric population, comparatively lower than in adults. They cause frameshift insertions and deletions at the C-terminus, resulting in altered localisation by removal of one or two nuclear localisation signals. Co-existence with FLT3-ITD mutations is common. NPM1 mutations have a favourable prognosis [15]. Mutated CEBPA is detected in about 18% of paediatric AML patients, which is comparable to the incidence in adult AML; it can be monoallelic or biallelic [16]. Biallelic CEBPA mutations often result from a homozygous mutation or a compound heterozygous mutation, where different mutations occur on each allele. Biallelic CEBPA mutations in AML are associated with a better prognosis.

Relapse in paediatric AML refers to the recurrence of leukaemic cells (blasts ≥5%) after the child has achieved complete remission. Although outcomes for newly diagnosed paediatric cases have improved over the past 20 years, more than one-third of patients continue to relapse and experience suboptimal long-term outcomes [17]. Relapse is common in patients with high-risk mutations such as FLT3-ITD and TP53. In some cases, treatment-resistant cells can be detected as MRD, which is often used to predict relapse. The identification of these tumour-resistant cells and their relation to normal progenitors remains mysterious, thereby limiting the development of targeted therapies for paediatric AML [18]. Survival after relapse is significantly lower than in newly diagnosed AML.

The therapy of paediatric AML is still based on intensive chemotherapy and, if necessary, allogeneic haematopoietic stem cell transplantation (allo-HSCT) [19]. Induction therapy should include two courses of induction based on an anthracycline (daunorubicin or idarubicin) and a nucleoside analogue (usually cytarabine). Various gene-targeted therapies, such as FLT3 inhibitors, are being incorporated into chemotherapy regimens and are undergoing ongoing clinical trials [7]. The number of courses of chemotherapy needed to minimise relapse risk without increasing toxicity remains controversial [20]. Flow cytometric assessment of MRD has been used prospectively to adapt therapy and has been analysed retrospectively in several clinical trials for childhood AML [20]. In case of relapse, all patients are indicated for allo-HSCT [19]. There are various articles published on paediatric AML, and summaries of a few cases are discussed below [Table/Fig-13] [21-29].

Author name, year	Age	Chief complaints	Mutational studies	IHC status/ flowcytometry	Follow-up details
Li T et al., 2024 [21]	2 years (one patient in series)	Decreased appetite, malaise, respiratory distress due to cardiac tamponade	Not specified for that specific patient	AML confirmed by flow cytometry and immunotyping	Postchemo remission in 2.5 years
Wang L et al., 2025 [22]	11 years (one patient in series)	Persistent cervical lymphadenopathy, abnormal blood counts	NUP98-R fusion, frequent FLT3-ITD, IDH1/2 mutations-fusion detected by targeted sequencing	AML confirmed by flow cytometry	Patient achieved complete remission with targeted therapy + transplant
Zhang HX et al., 2025 [23]	4 months	High-grade fever and diarrhoea, leukocytosis, blasts in peripheral blood	Complex karyotype (48,XY,+13,+19/..., del p12); GNB1 G116S Tier-II mutation detected	Leukaemic cells positive for HLA-DR, CD4, CD7, CD33, CD34, CD117, CD123	No chemo given (family declined); died of respiratory failure at 26 days
Guo Y et al., 2021 [24]	12 years, 5 months	Fever, pallor, hepatosplenomegaly, pancytopenia	FANCC & AKAP9 mutations	AML positive via flowcytometry; IHC noted CD7-/MPO- on bone marrow biopsy	Died of sepsis 3 weeks postchemo
Araújo NS et al., 2018 [25]	9 years	Fever, fatigue, oral petechiae; initial APL later scalp lesion	t(15;17) translocation; PML/RARA fusion by molecular testing	Positive for MPO, CD45, TdT	Achieved remission with All-Trans Retinoic Acid + chemo
Tripathi Y et al., 2018 [26]	7 years	Fever, bilateral leg pain, urinary incontinence, limb paresis with CNS masses on CT	Not specifically reported	Positive for MPO, LCA, MIC-2	Achieved morphological remission after induction; residual CNS lesions >90% reduced
Liu Y et al., 2021 [27]	12 yrs (Patient 2)	Intermittent fever, fatigue, malaise	t(6;11) (q27;q23) → KMT2A-MLLT4 fusion	Blasts positive for CD33, CD11c, CD34, CD117, CD13, CD11b, CD7; MPO negative → AML M0 phenotype	High-risk; candidate for allogeneic HCT in complete remission
Eason AC et al., 2019 [28]	6 months	Multiple skin nodules/ leukaemia cutis	t(8;19)(p11.2;q13.3) translocation; KAT6A rearrangement by FISH	IHC positive for CD68, MPO confirming monocytic lineage	Achieved remission with standard AML regimen
Gaál Z et al., 2021 [29]	8 months (Case 1)	Rapidly growing mandibular mass	Not specifically reported	Blasts positive for CD13, CD33, cytoplasmic MPO; negative for CD34, HLA-DR → APL-like immunophenotype	Not specified; managed according to APL protocols

[Table/Fig-13]: Review of some of the previously published articles on paediatric AML [21-29].
FANCC: Fanconi anaemia complementation group C; AKAP9: A-kinase anchoring protein 9; PML: Promyelocytic leukaemia; RARA: Retinoic acid receptor alpha gene; MLLT4: Mixed-lineage leukaemia translocated to 4, KMT2A: Lysine methyltransferase 2A; KAT6A: Lysine acetyltransferase 6A

CONCLUSION(S)

Paediatric AML is a rare but aggressive, complex and heterogeneous disease. Molecular diagnostics play an important role in the classification, diagnosis, risk stratification, treatment and prognosis of AML. Early identification of high-risk patients can improve outcomes through tailored treatment plans. Future research should focus on personalised treatment strategies and novel therapeutic approaches to further enhance survival rates and quality of life. Survivorship care is essential, as long-term complications from treatment can affect quality of life.

REFERENCES

[1] Padmakumar D, Chandraprabha VR, Gopinath P, Vimala Devi ART, Anitha GRJ, Sreelatha MM, et al. A concise review on the molecular genetics of acute myeloid leukaemia. Leuk Res. 2021;111:106727. Doi: 10.1016/j.leukres.2021.106727. Epub 2021 Oct 16. PMID: 34700049.

[2] Kurzer JH, Weinberg OK. Updates in molecular genetics of acute myeloid leukaemia. Semin Diagn Pathol. 2023;40(3):140-51. Doi: 10.1053/j.semdp.2023.04.002. Epub 2023 Apr 7. PMID: 37059636.

[3] Koulmane Laxminarayana SL, Kohli S, Agrohi J, Belurkar S. Pediatric non-down syndrome acute megakaryoblastic leukaemia with unusual immunophenotype. Cureus. 2023;15(3):e35965. Doi: 10.7759/cureus.35965. PMID: 36911590; PMCID: PMC9999050.

[4] Surapally S, Tenen DG, Pulikkan JA. Emerging therapies for inv(16) AML. Blood. 2021;137(19):2579-84. Doi: 10.1182/blood.2020009933. PMID: 33821975; PMCID: PMC8120144.

[5] Schwede M, Rodriguez G, Kennedy VE, Henry S, Wood D, Mannis GN, et al. The improved prognosis of FLT3-internal tandem duplication but not tyrosine kinase domain mutations in acute myeloid leukaemia in the era of targeted therapy: A real-world study using large-scale electronic health record data. Haematologica. 2025 Feb 6. Doi: 10.3324/haematol.2024.286695. Epub ahead of print. PMID: 39911116.

[6] Krock B, Oberley MJ. Molecular genetics of pediatric acute myeloid leukaemia. Clin Lab Med. 2021;41(3):497-515. Doi: 10.1016/j.cll.2021.03.014. Epub 2021 Jul 1. PMID: 34304778.

[7] Park HS. What is new in acute myeloid leukaemia classification? Blood Res. 2024;59(1):15. Doi: 10.1007/s44313-024-00016-8. PMID: 38616211; PMCID: PMC11016528.

[8] Kiyoi H, Kawashima N, Ishikawa Y. FLT3 mutations in acute myeloid leukaemia: Therapeutic paradigm beyond inhibitor development. Cancer Sci. 2020;111(2):312-22. Doi: 10.1111/cas.14274. Epub 2019 Dec 30. PMID: 31821677; PMCID: PMC7004512.

[9] Desikan SP, Daver N, DiNardo C, Kadia T, Konopleva M, Ravandi F. Resistance to targeted therapies: Delving into FLT3 and IDH. Blood Cancer J. 2022;12(6):91. Doi: 10.1038/s41408-022-00687-5. PMID: 35680852; PMCID: PMC9184476.

[10] Wick N, Hitto I, Welder D, Slone T, Koduru P, Fuda F, et al. Acute myeloid leukaemia with RAM immunophenotype presenting with extensive mesenteric and retroperitoneal lymphadenopathy: A case report and review of the literature. Leuk Res Rep. 2021;17:100287. Doi: 10.1016/j.lrr.2021.100287. PMID: 34976721; PMCID: PMC8683846.

[11] Huang BJ, Smith JL, Wang YC, Taghizadeh K, Leonti AR, Ries RE, et al. CBFB-MYH11 fusion transcripts distinguish acute myeloid leukaemias with distinct molecular landscapes and outcomes. Blood Adv. 2021;5(23):4963-68. Doi: 10.1182/bloodadvances.2021004965. PMID: 34547772; PMCID: PMC9153007.

[12] Panda S, Wang Y, Richter L, Becker M, Garrett LJ, Rivas C, et al. CBFB-MYH11 is required for the maintenance of Inv(16) AML. Blood. 2022;140(Suppl 1):2995-96. Doi: 10.1182/blood-2022-169475.

[13] Quessada J, Cuccuini W, Saultier P, Loosveld M, Harrison CJ, Lafage-Pochitaloff M. Cytogenetics of pediatric acute myeloid leukaemia: A review of the current knowledge. Genes (Basel). 2021;12(6):924. Doi: 10.3390/genes12060924. PMID: 34204358; PMCID: PMC8233729.

[14] Wan CL, Huang YH, Huang SM, Xu YL, Tan KW, Yan-Qiu, et al. Investigations of the prognostic value of RUNX1 mutation in acute myeloid leukaemia patients: Data from a real-world study. Leuk Res. 2024;139:107483. Doi: 10.1016/j.leukres.2024.107483. Epub 2024 Mar 12. PMID: 38493755.

[15] Tregnago C, Benetton M, Padrin D, Polato K, Borella G, Da Ros A, et al. NPM1 mutational status underlines different biological features in pediatric AML. Cancers (Basel). 2021;13(14):3457. Doi: 10.3390/cancers13143457. PMID: 34298672; PMCID: PMC8304368.

[16] Liao XY, Fang JP, Zhou DH, Qiu KY. CEBPA are independent good prognostic factors in pediatric acute myeloid leukaemia. Hematol Oncol. 2022;40(2):258-68. Doi: 10.1002/hon.2951. Epub 2021 Nov 27. PMID: 34816468.

[17] Egan G, Tasian SK. Relapsed pediatric acute myeloid leukaemia: state-of-the-art in 2023. Haematologica. 2023;108(9):2275-88. Doi: 10.3324/haematol.2022.281106. PMID: 36861399; PMCID: PMC10483345.

[18] Keyes TJ, Jager A, Krueger M, Plevritis S, Tibshirani R, Aplenc R, et al. Improved relapse prediction in pediatric acute myeloid leukaemia by deconvolving lineage-specific and cancer-specific features in single-cell data. Blood. 2022;140(Suppl 1):6288-89.

[19] Reinhardt D, Antoniou E, Waack K. Pediatric acute myeloid leukaemia-past, present, and future. J Clin Med. 2022;11(3):504. Doi: 10.3390/jcm11030504. PMID: 35159956; PMCID: PMC8837075.

[20] Rubnitz JE, Kaspers GJL. How I treat pediatric acute myeloid leukaemia. Blood. 2021;138(12):1009-18. Doi: 10.1182/blood.2021011694. PMID: 34115839.

[21] Li T, Tang X, He X, Zhang L, Zhang Y, Wang L, et al. Case report: Clinical features of pediatric acute myeloid leukaemia presenting with cardiac tamponade: A case series study and literature review. Front Oncol. 2024;14:1391768. Doi: 10.3389/fonc.2024.1391768

[22] Wang L, Chen S, Shen Y, Si P. BCORL1 S878G, GNB1 G116S, SH2B3 A536T, and KMT2D S3708R tetramutation co-contribute to a pediatric acute myeloid leukaemia: Case report and literature review. Front Pediatr. 2022;10:993952. Doi: 10.3389/fped.2022.993952.

[23] Zhang HX, Xiong RJ, Yin TT, Pan HY, Jin RM. From low remission to hope: The efficacy of targeted therapies in NUP98-R positive pediatric acute myeloid leukaemia. World J Pediatr. 2025;21(3):266-73. Doi: 10.1007/s12519-025-00875-w.

[24] Guo Y, Liao X, Zou P, Xiao J. Acute myeloid leukaemia arising from Fanconi anemia in a 12-year-old boy: A case report. AME Case Rep. 2021;5:29. Doi: 10.21037/acr-20-151.

[25] Araújo NS, dos Santos Júnior CJ, da Silva Gomes VM, Calheiros Leite LA, Bomfim LN, Gusmão AKFDS, et al. A rare case of relapsed pediatric acute promyelocytic leukaemia with skin involvement by myeloid sarcoma. Am J Case Rep. 2018;19:438-41. Doi: 10.12659/AJCR.907847.

[26] Tripathi Y, Sharma P, Verma R, Singh K. Acute myeloid leukaemia presenting as central nervous system myeloid sarcoma in a child. J Pediatr Hematol Oncol. 2018;40(6):e360-e363. Doi: 10.1097/MPH.0000000000001234.

[27] Liu Y, GuLiBaHa M, Yue YB, Li MW, Cao SB, Yan M. An isolated childhood myeloid sarcoma with germline MSH6 mutation- A case report. Transl Pediatr. 2021;10(8):2136-43. Doi: 10.21037/tp-21-326.

[28] Eason AC, Bunting S, Peterson JF, Saxe D, Sabnis HS. Acute myeloid leukaemia in an infant with t(8;19)(p11.2;q13.3) translocation: Case report and review of the literature. Case Rep Hematol. 2019;2019:4198415. Doi:10.1155/2019/4198415.

[29] Gaál Z, Jakab Z, Kárai B, Ujfalusi A, Petrás M, Kállay K, et al; Hungarian Pediatric Oncology-Hematology Group. Recent advances in the management of pediatric acute myeloid leukaemia- Report of the Hungarian Pediatric Oncology-Hematology Group. Cancers (Basel). 2021;13(20):5078. Doi: 10.3390/cancers13205078.

PARTICULARS OF CONTRIBUTORS:

1. Postgraduate Student, Department of Pathology, Madras Medical College, Chennai, Tamil Nadu, India.
2. Assistant Professor, Department of Pathology, Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India.
3. Professor and Head, Department of Pathology, Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India.
4. Assistant Professor, Department of Pathology, Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India.
5. Senior Scientist, Department of Pathology, Institute of Child Health and Hospital for Children, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. M Dougul Regis,
A Block, No.15, Institute of Child Health and Hospital for Children, Egmore,
Chennai, Tamil Nadu, India.
E-mail: dougulregis@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: May 13, 2025
- Manual Googling: Jul 21, 2025
- iThenticate Software: Jul 29, 2025 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **May 12, 2025**
Date of Peer Review: **Jun 17, 2025**
Date of Acceptance: **Jul 30, 2025**
Date of Publishing: **Oct 01, 2025**