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Case Report

Congenital Acute Myeloid Leukemia: A Series of Three Cases

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Abstract

Congenital acute myeloid leukemia (C-AML) is a rare and aggressive hematologic malignancy diagnosed within the first month of life. It represents significant diagnostic and therapeutic challenges due to its nonspecific clinical presentation and the limited tolerance of neonates to intensive chemotherapy. Trisomy 21 is the most frequently associated chromosomal abnormality, and GATA1 mutations play a key role in leukemogenesis in this context. We report a retrospective, descriptive series of three male neonates diagnosed with C-AML at a single tertiary care center between 2011 and 2026. All three presented with dysmorphic facial features suggestive of trisomy 21, respiratory distress, and cutaneous or systemic involvement, with varying degrees of cytopenia and marked hyperleukocytosis. Immunophenotyping confirmed acute megakaryoblastic leukemia (AML M7) in two infants, both with aberrant CD7 expression, and AML M2 in the third. All three also had congenital heart defects. Management included supportive care, and chemotherapy where feasible. All patients died during the neonatal period. These cases illustrate the aggressive course and diagnostic complexity of C-AML. Early clinical suspicion, particularly in neonates with syndromic features such as Down syndrome, is essential. Prompt immunophenotypic confirmation, cardiac assessment before any chemotherapy, individualized supportive care, and multidisciplinary neonatal–hematologic management are critical to improving outcomes.

Keywords

Congenital Leukemia, Acute Myeloid Leukemia, Neonate, Down Syndrome, Immunophenotyping, Neonatal Oncology

1. Introduction

Congenital acute myeloid leukemia (C-AML) is a rare and aggressive hematologic malignancy diagnosed within the first 28 days of life. It accounts for less than 1% of all pediatric leukemias, yet carries a disproportionately high burden of morbidity and mortality. The disease often presents with non-specific symptoms, such as respiratory distress, hepatosplenomegaly, or skin lesions, that mimic more common neonatal conditions like sepsis, congenital infections, or metabolic disorders. This clinical ambiguity frequently delays diagnosis, thereby compromising the window for timely therapeutic intervention.

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Unlike leukemias in older children, C-AML presents unique diagnostic and therapeutic challenges due to the immaturity of neonatal organ systems and the limited data available to guide treatment. While associations with genetic syndromes, particularly Down syndrome, are well established, the pathogenesis remains incompletely understood. Most of the current knowledge derives from isolated case reports and small case series, underscoring the critical need for cumulative clinical documentation and analysis.

2. Materials and Methods

This retrospective, descriptive, single-center study was conducted at the Ibn Rochd University Hospital in Casablanca, Morocco. We reviewed all neonates diagnosed with C-AML, defined as acute myeloid leukemia diagnosed within the first 28 days of life, over the period from January 2011 to September 2026.

Patient data were extracted from medical records and included the following variables:

1) Demographic characteristics (sex, gestational age, family history)
2) Maternal and perinatal history
3) Clinical presentation at admission
4) Laboratory findings including complete blood count (CBC), bone marrow myelogram, immunophenotyping, and polymerase chain reaction (PCR) analyses
5) Imaging studies, such as ultrasound, echocardiography, and radiographs
6) Therapeutic interventions, including supportive care and chemotherapy
7) Clinical outcomes, including mortality and discharge status

Immunophenotyping was performed to confirm the diagnosis and classify the AML subtype in all cases.

3. Results

3.1. Case 1

A male neonate was born to non-consanguineous parents after an unmonitored full-term pregnancy. The mother, gravida II para II, was Rhesus-negative and had received anti-D prophylaxis after each delivery; serological screening had not been performed. Maternal history was notable for intrapartum fever. The infant was admitted on day 8 of life for suspected sepsis.

Ecchymotic lesions of the right foot were present at birth. On day 3 of life, he developed fever with necrotic lesions; he was seen by a general practitioner, who prescribed an undocumented treatment. He was subsequently referred to our center because of clinical deterioration.

On examination he had dysmorphic (trisomic) facies, generalized hypotonia, lethargy, fever, tachypnea, tachycardia, grey skin, delayed capillary refill (6 seconds), and respiratory distress. A systolic murmur, marked hepatosplenomegaly (liver edge 4 cm below the costal margin; spleen palpable 4 finger-breadths below the costal margin), and ecchymotic, necrotic lesions of all five toes of the right foot were noted.

Laboratory investigations showed bicytopenia and hyperleukocytosis (white blood cell count 250 $\times 10^9$/L) with 71% circulating blasts; immunophenotyping was consistent with AML M2. Echocardiography identified an atrial septal defect without right-heart dilation or pulmonary hypertension. Doppler ultrasound demonstrated thrombosis of the infrarenal aorta and both iliac vessels, more pronounced on the right.

Management included surgical amputation of the right forefoot with necrosectomy of the second left toe, anticoagulation, and broad-spectrum antibiotics (ceftazidime, teicoplanin, fluconazole). Chemotherapy with cytarabine (200 mg/m²) was initiated, but the patient died at 21 days of life.

3.2. Case 2

A male neonate, also born to non-consanguineous parents after a poorly monitored term pregnancy, was hospitalized in pediatric surgery on day 2 of life for neonatal intestinal obstruction secondary to Hirschsprung's disease, managed with a diverting colostomy. He was readmitted at 15 days of life with respiratory distress, poor feeding, and general deterioration.

On examination he had dysmorphic (trisomic) facies, marked pallor, hypotonia, respiratory distress, hepatomegaly (liver edge 3 cm below the costal margin), and a well-healed surgical scar with colostomy. A cardiac murmur with gallop rhythm and a generalized mucocutaneous rash with erythematous, vesicular, and crusted lesions predominating on the face were also noted.

Laboratory investigations revealed bicytopenia, normocytic normochromic anemia, and hyperleukocytosis (white blood cell count 182 $\times 10^9$/L) with 45% circulating blasts. HSV and CMV PCR were negative. Bone marrow examination showed 70% blasts, consistent with acute leukemia; immunophenotyping confirmed acute megakaryoblastic leukemia (AML M7) with aberrant CD7 expression.

Abdominal ultrasound showed homogeneous hepatomegaly, gallbladder microlithiasis, and a small right paracolic effusion. Echocardiography revealed a 2 mm ventricular septal defect with moderate pericardial effusion.

The infant received supportive care and broad-spectrum antibiotics (imipenem-cilastatin, colistin, amikacin). Chemotherapy was planned pending clinical stabilization, but he died on day 38 of life before treatment could begin.

3.3. Case 3

A male neonate was born to non-consanguineous parents; the mother was 40 years old, gravida VI para IV, with two prior miscarriages, and was Rhesus-positive. The pregnancy was poorly monitored, with no antenatal serological testing,

and was complicated by spontaneous preterm labor at 36 weeks of unclear etiology.

The infant adapted poorly to extrauterine life, with Apgar scores of 6 and 7 at 1 and 5 minutes, respectively, and was admitted to the neonatal intensive care unit on the day of birth for respiratory distress with expiratory grunting.

On examination he was conscious and reactive but hypotonic, with a dysmorphic facial appearance suggestive of trisomy, tachypnea, respiratory distress (Silverman score 5/10), normal heart rate, and preserved capillary refill. A systolic murmur, generalized edema, and moderate ascites were present, with preserved diuresis; blood pressure was 70/25 mmHg (mean arterial pressure 40 mmHg). There was no hepatosplenomegaly. Chest radiography showed an alveolar syndrome with good thoracic compliance and a small pleural effusion, without pneumothorax.

Laboratory findings revealed bicytopenia with leukocytosis (white blood cell count 198 $\times 10^9$/L); infection markers were negative. Immunophenotyping confirmed acute megakaryoblastic leukemia (AML M7) with aberrant CD7 expression. Echocardiography showed a large (7 mm) ventricular septal defect, a significant patent ductus arteriosus with left-to-right shunt, a 5 mm ostium secundum atrial septal defect, and signs of pulmonary hypertension. Cranial ultrasound was normal.

The infant required intubation and mechanical ventilation. Empirical antibiotics (ceftriaxone, gentamicin) were started alongside supportive treatment with sildenafil, dobutamine, paracetamol, albumin, and furosemide. On day 4 the course was complicated by alveolar hemorrhage and signs of sepsis, managed with transfusions of fresh frozen plasma and platelets, norepinephrine, corticosteroids (hydrocortisone hemisuccinate), and a second-line antibiotic regimen (imipenem-cilastatin, colistin, amikacin). Despite resuscitation, he died of refractory respiratory failure on day 11 of life.

4. Discussion

Congenital leukemia is a rare hematologic malignancy that arises in utero, with diagnosis typically made in the first 28 days of life [1]. It accounts for less than 1% of all pediatric leukemias [1] and represents the third most common neonatal malignancy after teratomas and neuroblastomas [2]. The incidence is estimated to be 1 per 5 million live births [3]. Unlike leukemias in older children, which are predominantly lymphoid, most cases of Congenital Leukemia are myeloid [3].

The etiopathogenesis of C-AML remains poorly understood, with both genetic predisposition and environmental factors during fetal development implicated in leukemogenesis. Trisomy 21 is the most frequently observed chromosomal associated with congenital leukemia and is linked to a 10- to 20-fold increase in the risk of developing acute leukemia [4]. Several other genetic syndromes—including Turner syndrome, Klippel-Feil syndrome, Ellis-van Creveld syndrome, and other trisomies (such as trisomy 1, 8, 9, 13, and 19) have also been reported [5]. Environmental factors such as maternal infections, intrauterine exposure to radiation or toxins, elevated insulin-like growth factor-1 (IGF-1) levels and certain medications during pregnancy have been proposed as potential contributors, however, their definitive role remains unclear due to the rarity and heterogeneity of reported cases [6].

Several studies have shown an increased incidence of leukemia in individuals with Down syndrome, underscoring the central role of trisomy 21 in leukemogenesis. This risk has been linked to impaired hematopoiesis, dysregulated granulopoiesis, immunodeficiency, abnormal cell-cycle kinetics, increased susceptibility to viral transformation, a tendency toward chromosomal nondisjunction and instability, and deficient DNA repair mechanisms [7]. These same abnormalities underlie the risk of transient myeloproliferative disorder (TMD), estimated at 10% among neonates with Down syndrome [8].

TMD and C-AML differ in several key respects. TMD typically resolves spontaneously within the first three months of life, whereas C-AML is a more aggressive condition marked by higher blast counts, rapid progression, and organ infiltration [3]. Both TMD and Down-syndrome-associated acute megakaryoblastic leukemia (AMKL) are defined by somatic N-terminal truncating mutations in GATA1, a zinc-finger transcription factor essential for normal erythroid and megakaryocytic differentiation. These mutations produce an exclusively truncated isoform, GATA1s, which lacks the N-terminal activation domain and alters transcriptional regulation of downstream targets. Such mutations are highly specific of hematologic disorders arising in the context of trisomy 21. GATA1 mutations alone are insufficient to initiate leukemogenesis; however, within the fetal hematopoietic environment — particularly the liver — GATA1s-expressing progenitors show increased proliferative capacity and impaired differentiation, conferring a selective clonal advantage. This context-dependent effect illustrates the interaction between GATA1 mutations and the altered hematopoietic milieu of trisomy 21, together establishing a preleukemic state susceptible to additional transforming events [9].

The real challenge is that C-AML often presents with non-specific signs such as fever, anemia, failure to thrive, lethargy, hepatosplenomegaly, petechiae and cutaneous involvement such as “blueberry muffin” rash, indicative of extramedullary hematopoiesis. Early recognition of these signs, particularly in neonates with known chromosomal or syndromic anomalies, is essential for timely diagnosis and management [10].

The diagnostic criteria of C-AML include onset within the first month of life, proliferation of immature myeloid cells, infiltration of non-hematopoietic tissues by blasts, and exclusion of other causes such as TMD, blood group incompatibility, leukemoid reactions, congenital syphilis, and TORCH [4].

The treatment of C-AML remains highly challenging due to the neonatal physiological immaturity, particularly in the immune system and vital organs, which heightens their sensitivity to the toxicity of standard chemotherapeutic agents. Alt-

hough chemotherapy can induce remission in some cases, others experience rapid progression and early death, reflecting the narrow therapeutic window and the need for individualized management strategies. Anthracyclines, commonly used in AML induction regimens, pose particular risk in neonates with Down syndrome, given their high prevalence of congenital heart defects and increased susceptibility to cardiotoxicity [11]. As a result, thorough cardiac assessment, including echocardiography, is crucial prior to initiating therapy. Clinical presentation strongly influences therapeutic decisions: in stable neonates without severe symptoms or organ dysfunction, a conservative "wait and see" approach combined with supportive care may be appropriate [12, 13]. Conversely, in cases of aggressive presentation marked by hyperleukocytosis, hepatic impairment, or multiorgan failure, low-dose cytarabine may be administered to reduce leukemic burden while limiting toxicity [14]. These complexities highlight the need for individualized, carefully balanced treatment strategies in this vulnerable population.

Hematopoietic stem cell transplantation (HSCT) has emerged as a potential curative option for high-risk or relapsed C-AML. While historically associated with high treatment-related mortality in neonates, advances in transplant techniques and supportive care have improved its safety and feasibility. Reduced-intensity conditioning regimens are now being explored to lower toxicity while maintaining disease control. Additionally, newer strategies such as T-cell depletion, umbilical cord blood transplantation, and post-transplant maintenance therapies (e.g., FLT3 inhibitors or hypomethylating agents) have expanded donor options and reduced the risk of graft-versus-host disease. Nevertheless, determining the optimal timing for HSCT remains complex, as the procedure must be balanced against the neonate's capacity to withstand both the conditioning regimen and transplant-related complications [3].

Despite therapeutic advances, the overall prognosis for C-AML remains poor. The two-year survival rate is estimated at approximately 23% [15], and most newborns are unable to tolerate the full course of induction therapy. There is an urgent need for less toxic, more targeted treatment strategies, and further research is essential to identify effective therapies that are safe for neonatal patients. Clinical trials focusing on novel agents, age-adapted protocols, and optimized transplant regimens may eventually improve outcomes for this vulnerable population.

5. Conclusions

Congenital acute myeloid leukemia remains a rare but highly lethal neonatal malignancy, frequently associated with genetic syndromes such as trisomy 21. Its nonspecific and often misleading clinical presentation delays diagnosis and limits treatment options in a population already vulnerable to the toxicity of chemotherapy. The cases described here illustrate the clinical heterogeneity of C-AML and underscore the need for a high index of suspicion, particularly in neonates with dysmorphic features or unexplained cytopenia.

While advances in immunophenotyping and supportive care have improved diagnostic precision, prognosis remains poor, with high early mortality. Collaborative research is needed to better understand the etiopathogenesis of C-AML and to develop targeted, less toxic therapies feasible in the neonatal period. Until such advances are realized, early recognition, multidisciplinary management, and individualized therapeutic strategies remain the most effective tools for improving survival.

Abbreviations

C-AML	Congenital Acute Myeloid Leukemia
AML	Acute Myeloid Leukemia
AMKL	Acute Megakaryoblastic Leukemia
TMD	Transient Myeloproliferative Disorder
HSCT	Hematopoietic Stem Cell Transplantation
PCR	Polymerase Chain Reaction
CBC	Complete Blood Count
HSV	Herpes Simplex Virus
CMV	Cytomegalovirus

Author Contributions

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Data Availability Statement

The data supporting the outcome of this research work has been reported in this manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

References

[1] Tsujimoto, H., Kounami, S., Mitani, Y., Watanabe, T., Takifuji, K. Neonatal Acute Megakaryoblastic Leukemia Presenting with Leukemia Cutis and Multiple Intracranial Lesions Successfully Treated with Unrelated Cord Blood Transplantation. Case Reports in Hematology. 2015, 2015, 610581. https://doi.org/10.1155/2015/610581

[2] Karczmarzyk, Z., Szuba, M., Krupa, J., Czaplińska, N., Kociszewska-Najman, B. Congenital Leukemia: Presentation of Three Cases. Cureus. 2025. https://doi.org/10.7759/cureus.95318

[3] Alsharidah, S., Almatar, E. Congenital Acute Myeloid Leukemia (AML): A Case Report. International Medical Case Reports Journal. 2025, 18, 585-590. https://doi.org/10.2147/IMCRJ.S499579

[4] Shrivastava, J. P., Magnani, K. K., Tripathi, L., Mangal, K. S. Congenital Acute Myeloid Leukemia: A Rare Diagnostic Enigma — Case Report with Review of Literature. South Asian Journal of Cancer. 2016, 5(4), 212-213. https://doi.org/10.4103/2278-330X.195349

[5] Isaacs, H. Jr. Fetal and Neonatal Leukemia. Journal of Pediatric Hematology/Oncology. 2003, 25(5), 348-361. https://doi.org/10.1097/00043426-200305000-00002

[6] Sanvisens, A., Bueno, C., Calvete, O., Solé, F., Marcos-Gragera, R., Solans, M. Prenatal and Perinatal Factors Associated with Infant Acute Lymphoblastic Leukaemia: A Scoping Review. Cancers. 2025, 17(3), 370. https://doi.org/10.3390/cancers17030370

[7] Mason, N. R., Cahill, H., Diamond, Y., McCleary, K., Kotecha, R. S., Marshall, G. M., Mateos, M. K. Down Syndrome-Associated Leukaemias: Current Evidence and Challenges. Therapeutic Advances in Hematology. 2024, 15, 20406207241257901. https://doi.org/10.1177/20406207241257901

[8] Laurent, A. P., Kotecha, R. S., Malinge, S. Gain of Chromosome 21 in Hematological Malignancies: Lessons from Studying Leukemia in Children with Down Syndrome. Leukemia. 2020, 34(8), 1984-1999. https://doi.org/10.1038/s41375-020-0854-5

[9] Takasaki, K., Wafula, E. K., Fan, J. M., Sit, Y. T., Kumar, S. S., Smith, D., Gagne, A., Gearhart, P. A., French, D. L., Thom, C. S., Chou, S. T. Single-Cell Transcriptomics Reveal Individual and Cooperative Effects of Trisomy 21 and GATA1s on Hematopoiesis. *Stem Cell Reports*. 2025, 20(8), 102577. https://doi.org/10.1016/j.stemcr.2025.102577

[10] Bustamante-Ordoñez, M. A., Macavilca-Toribio, M. A., Arenas-Vasquez, J. R., Roman-Lazarte, V., Zavaleta-Corvera, C., Samanez-Obeso, Á. Extreme Hyperleukocytosis and Blueberry Muffin Skin Lesions as the Initial Presentation of Neonatal Leukemia: A Case Report. BMC Pediatrics. 2026, 26, 695. https://doi.org/10.1186/s12887-026-06995-0

[11] O'Brien, M. M., Taub, J. W., Chang, M. N., et al. Excessive Cardiotoxicity Despite Excellent Leukemia-Free Survival for Pediatric Patients with Down Syndrome and Acute Myeloid Leukemia: Results from POG (Pediatric Oncology Group) Protocol 9421. Blood. 2006, 108(11), Abstract 559.

[12] Yang, W., Sui, S., Hao, S. Spontaneous Remission of Congenital Acute Megakaryoblastic Leukemia in a Neonate with Down Syndrome. Open Medicine. 2026, 21(1), 20251367. https://doi.org/10.1515/med-2025-1367

[13] Yasudome, Y., Nakagawa, S., Nagahama, J., Nakamura, T., Abematsu, T., Kodama, Y., Nishikawa, T., Okamoto, Y. Spontaneous Remission in a Case of Neonatal Leukemia with KMT2A Gene Rearrangement. Pediatric Blood & Cancer. 2024, 71(10), e31235. https://doi.org/10.1002/pbc.31235

[14] Johann, P., Dabek, M. T., Heinzmann, T., Westhoff, J., Kulozik, A., Kunz, J. Excessive Toxicity After Treatment of Congenital Acute Myeloid Leukemia. Klinische Pädiatrie. 2019, 231(6), 291-293. https://doi.org/10.1055/a-0859-7375

[15] Bresters, D., Reus, A. C. W., Veerman, A. J. P., van Wering, E. R., van der Does-van den Berg, A., Kaspers, G. J. L. Congenital Leukaemia: The Dutch Experience and Review of the Literature. British Journal of Haematology. 2002, 117(3), 513-524. https://doi.org/10.1046/j.1365-2141.2002.03459.x