CHAPTER

# 31

# Neonatal Leukemia

Anirban Das, Akanksha Chichra, Anupama Borker

## INTRODUCTION

Leukemia is an infrequent cancer in the neonatal period.[1] Solid tumors, including neuroblastoma, outnumber hematological malignancies in this age group.[2] However, it remains the second most common malignancy in neonates.[3] Acute myeloid leukemia (AML) is more frequent than acute lymphoblastic leukemia (ALL).[2,3] A tumoral syndrome with hepatosplenomegaly and skin nodules (leukemia cutis) is frequent. The central nervous system (CNS) and lungs are important sites of extrahematopoietic involvement. High total leukocyte counts and presence of rearrangements of the mixed lineage leukemia (MLL) gene are other unique features. Overall the prognosis in this age group remains poor despite intensive therapy.[1-3]

The term "neonatal leukemia" is often used interchangeably with "congenital leukemia". The following diagnostic criteria have been proposed, viz. (1) presentation in the first 4 weeks of life, (2) proliferation of immature myeloid, lymphoid or erythroid cells, (3) infiltration of these cells into nonhematopoietic tissues and, (4) the absence of other diseases which might explain this proliferation.[4,5]

## EPIDEMIOLOGY

Neonatal leukemia accounts for less than 1% of all childhood leukemia.[2] Estimated incidence varies between 1–5 cases per million live births.[1] It is the leading cause of death from a malignancy in newborns.[3,6] In a retrospective study of leukemia during the first 3 months of life in Northern England, the incidence of acute leukemia was $8.6/10^6$ live births per year.[7] A higher frequency of AML (56–64%) than ALL (21–38%) has been reported in two large series of neonates with congenital leukemia.[3,5,8] Literature from India and South Asia remains confined to case reports and small series.[9-13]

## ETIOLOGY AND PATHOGENESIS

The biological differences in leukemia in neonates and infants led to the identification of several risk factors **(Box 31.1)**.

Identical twins have a high concordance rate for leukemia. Neonatal leukemia has been reported in association with Down, Turner, Klippel-Feil and Ellis-van Creveld syndromes as well as several trisomy disorders (trisomy 1, 8, 9, 13 and 19).[2,3] Epidemiological studies have correlated a decreasing incidence of low-birth-weight babies and an increased incidence of large-for-date newborns, to an increased incidence of infant ALL and AML.[14] A higher level of insulin-like growth factors, which may result in large-for-date babies, has been postulated to contribute to leukemogenesis.[3] Marcotte et al. have recently reported an increased risk of childhood ALL after prelabor cesarean delivery but not for emergency cesarean delivery, which was attributed to a maladaptive immune activation due to absence of stress response before birth.[15]

Maternal alcohol and marijuana use during pregnancy have been correlated with increased risk of infant leukemia.[2,3] The amount of maternal consumption of food containing DNA topoisomerase II inhibitors was correlated to the risk of developing MLL-rearranged AML.[16,17]

The link between MLL-rearrangement and neonatal or infant leukemia is quite strong.[1-3,5] The MLL gene located at 11q23 codes for a large histone methyltransferase that binds DNA and positively regulates gene transcription, including homeobox (HOX) genes.[18-20]

---

**Box 31.1** Putative associations for the development of neonatal leukemia

- *Chromosomal aberrations*: Trisomy 21 and others (1, 8, 9, 13, and 19)
- *Congenital syndromes*: Ellis-van Creveld, Klippel-Feil
- Identical twin with leukemia
- Large–for-date babies
- Prelabor elective cesarean section
- Maternal alcohol consumption in pregnancy
- Maternal marijuana use in pregnancy
- Maternal exposure to topoisomerase II inhibitors (flavonoids)

## CLINICAL FEATURES

Leukemia in neonates can present with a wide range of signs and symptoms. Antenatal ultrasound can detect hepatosplenomegaly, hydrops, and polyhydramnios as the initial presenting signs. Leukemia has been diagnosed in fetuses with Down syndrome (DS) as early as in the 33rd week of gestation.[3,21] Noonan syndrome (NS) can present with a similar MPD in utero.[22] Diagnosis is established by cord blood sampling.

Leukemia is an important cause of stillbirth.[3] The involved fetuses are often hydropic and macerated with enlarged and edematous placentae. Autopsy reveals leukemic infiltration in multiple organs. Extensive vascular involvement of the placenta by leukemic cells is attributed to cause fetal death.[23]

The unique presentation of neonatal leukemia is with nodular cutaneous infiltrates (leukemia cutis) described as a "blueberry muffin" baby **(Fig. 31.1)**.[2,3] They are also the initial presenting sign in about 50% of neonates, particularly those with AML-M5. It might be the initial clinical manifestation of disease and precede other signs of leukemia by up to 4 months. It may follow a waxing and waning course. In a cohort of Dutch neonates with congenital leukemia, the prevalence of leukemic skin infiltrates was 63.5%.[5] Leukemia in DS might present with a self-limiting vesicular pustular eruption, different from the typical "blueberry muffin" nodular infiltrates, which also harbor immature cells.[2,3]

Hepatosplenomegaly is a common finding in neonatal leukemia. Lymphadenopathy is observed less frequently.[5] CNS involvement is frequent.[2,3,5] A bulging fontanelle is the sign of meningeal leukemic infiltration or an intracranial bleed secondary to thrombocytopenia. Respiratory distress can be attributed to pulmonary hemorrhage and/or extensive leukemic infiltration complicated by atelectasis. Sepsis, pneumonia, and other infections are often the result of

neutropenia. Cardiac failure might develop with nonimmune hydrops secondary to severe anemia. Hyperviscosity and leukostasis might compromise CNS, cardiac and pulmonary functions.

## INVESTIGATIONS

Anemia, thrombocytopenia, leukocytosis or leukopenia with neutropenia and presence of blasts in the peripheral smear clinch the diagnosis. Hyperleukocytosis is present in a majority of the patients with a median leukocyte count of $104 \times 10^9$/L.[5] Bone marrow aspiration and biopsy need to be performed; however, it needs expertise to perform the procedure in a potentially sick neonate. Immunophenotyping from the bone marrow or even the peripheral blood sample helps distinguish AML from ALL. Acute leukemia of ambiguous lineage (ALAL) is commonly diagnosed in newborns based on the immunophenotyping criteria.[8] Cytogenetic studies help characterize the leukemia. Fluorescent in situ hybridization (FISH) helps in rapid diagnosis of MLL rearrangements.[1]

## DIFFERENTIAL DIAGNOSES

Neonatal leukemia needs to be differentiated from leukemoid reactions secondary to sepsis, hemolysis and hypoxia. Hepatosplenomegaly with anemia, thrombocytopenia and leukocytosis can occur in intrauterine infections, including toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis and human immunodeficiency virus (HIV). Differential diagnoses of cutaneous nodules in the neonate include congenital infections, neuroblastoma, rhabdomyosarcoma and histiocytosis.[2,3,5] Hepatic involvement with enlargement, fibrosis and multiple nodules of the liver, mimicking stage 4S neuroblastoma, has been described in AML-M7.[24] A list of common differential diagnoses is provided in **Box 31.2**.

## MANAGEMENT AND OUTCOMES FOR MAJOR SUBTYPES OF NEONATAL LEUKEMIA

Neonatal leukemia can be broadly classified and studied under the following heads:
- AML in neonates without DS
- ALL in neonates



**Figure 31.1** The baby presented on day 20 of life with generalized purplish skin nodules ("blueberry muffin" appearance), pallor and hepatosplenomegaly. Acute leukemia is one of the important differentials to consider in such cases

---

**Box 31.2** Differential diagnoses for neonatal leukemia

- *Intrauterine infections*: Toxoplasmosis, *cytomegalovirus*, rubella, herpes, syphilis and HIV
- *Postnatal infections*: Severe bacterial sepsis
- *Hematological disorders*: Blood group incompatibilities, twin-to-twin transfusion syndrome, alpha thalassemia, Diamond-Blackfan anemia, congenital dyserythropoietic anemia
- *Other malignancies*: Neuroblastoma, congenital rhabdomyosarcoma
- *Histiocytic disorders*: Langerhans cell histiocytosis, juvenile xanthogranuloma, hemophagocytic lymphohistiocytosis

*Abbreviation:* HIV, human immunodeficiency virus

- ALAL in newborns
- Transient abnormal myelopoiesis (TAM) in DS
- Juvenile myelomonocytic leukemia (JMML) and the myeloproliferative disease (MPD) in Noonan syndrome (NS) (MPD/NS).

## Acute Myeloid Leukemia in Neonates without Down Syndrome

Acute myeloid leukemia accounts for 75% of acute leukemia in the neonates. The common French-American-British (FAB) subtypes include M5 (50%), M4 (20%), M7 and M6. MLL rearrangements are reported in 25–40%.[2,3] Most frequently described ones are t(11;19)(q23;p13) and t(9;11)(p21;q23).[1] MLL-rearranged AML is correlated with the morphological subtypes acute myelomonoblastic leukemia (M4) and monoblastic leukemia (M5). These blasts demonstrate positivity for CD13, CD14, CD15 and CD33. Patients often present with high tumor load, which includes organomegaly in a high white blood cell (WBC) count and CNS involvement.[1,3,5,8] Patients with a t(6;11)(q27;q23) have higher median WBC counts than other MLL-rearranged AML.

In acute megakaryocytic leukemia (M7), immuno-phenotyping reveals positivity for platelet-associated antigens (CD36, CD41a, b, CD61). Bilateral periosteal reaction, osteolysis, myelofibrosis, liver and lymph nodal fibrosis are frequent. The presence of t(1;22)(p13;q13) translocation (20%) and RBM15-MKL1 fusion are reported, the former with better prognosis.[1,2,3,8]

Treatment of neonatal AML is based on anthracyclines and cytarabine with overall survival (OS) of 30%. Relapse rates are high (50%).[1]

Self-limiting forms of AML are described in neonates especially in cases of aleukemic leukemia cutis and in the absence of MLL rearrangement. Association with hemophagocytosis, t(8;16)(p11;p13) translocation and MYST3-CREBBP rearrangement, and a specific gene-expression profile has been described for some of these spontaneous remissions.[1] Pediatric t(8;16)(p11;p13) AML is a rare clinical entity associated with the FAB M4/M5 subtype and disruption of the MOZ (MYST3) and CBP (CREBBP) genes on chromosomes 8p11 and 16p13, respectively.[25,26] It is associated with spontaneous remissions. It has been recommended that in congenital AML, the presence of a MOZ-CBP fusion should be assayed at diagnosis. If detected and negativity of MRD achieved after induction, then close observation without further consolidation chemotherapy can be considered for such cases.[25,26]

## Acute Lymphoblastic Leukemia in Neonates

Acute lymphoblastic leukemia in infants is more often associated with a higher tumor load at diagnosis, a rearrangement in the MLL gene, and very immature B-cell phenotype (pro-B ALL) without CD10 expression **(Fig. 31.2)**. Neonatal ALL cells are more resistant to several standard chemotherapeutic agents and have been reported to have a
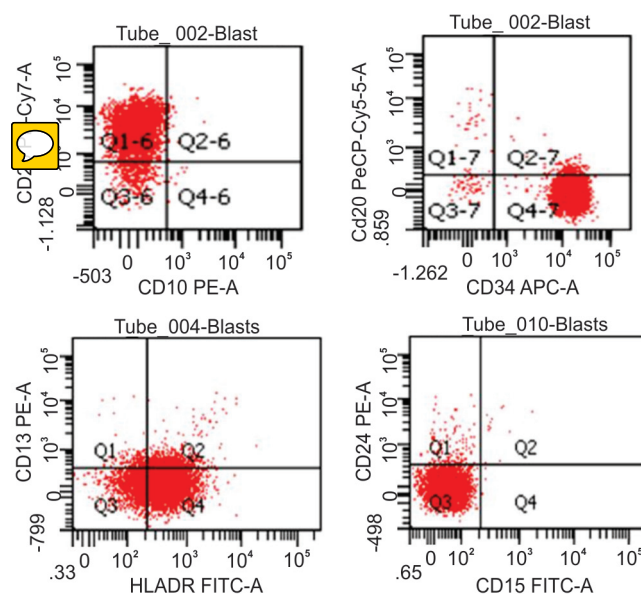


**Figure 31.2** Flow cytometry in neonatal acute lymphoblastic leukemia (ALL) often reveals expression of CD34, CD38, CD19 and CD9, with CD10 being negative, suggestive of a pro-B immunophenotype

very poor prognosis. Infants less than or equal to 3 months have 5-year event-free survival (EFS) of 42%.[1-3,5,8]

Linden et al. reported the outcome of 30 patients with congenital ALL treated with the interfant-99 protocol in 2009[27] with 2-year EFS of 20%. Hematopoietic stem-cell transplantation might have a role in therapy, since a high-risk group of infants younger than 6 months with MLL-rearranged ALL had better survival after receiving a transplant.[28]

## Acute Leukemia of Ambiguous Lineage in Newborns

Acute leukemia of ambiguous lineage including biphenotypic, bilineal and acute undifferentiated leukemia according to the World Health Organization (WHO) classification is a rare affecting both adults and children (including neonates) with a male predominance. In a series of 145 cases of perinatal leukemia, 10 cases (7%) of ALAL were reported.[3] Lineage switch from myeloid to lymphoid is attributed to selection of an initially occult clone following therapy targeting the dominant clone. About 93% have abnormal karyotypes, the most common being t(v;11q23). Most have a high WBC count and poor outcomes, even with HSCT.[29]

## Transient Abnormal Myelopoiesis in Neonates with Down Syndrome

Transient abnormal myelopoiesis seen in 5–10% of children with DS is characterized by clonally proliferated circulating blasts with megakaryoblastic or erythroblastic features, along with dyserythropoiesis and megakaryopoiesis. All children

harbor an acquired truncating GATA1 mutation, identical in type to those seen in myeloid leukemia of DS (ML-DS). Bone marrow examination is not helpful as the circulating blast count often exceeds the marrow count. Indeed there is strong evidence that the cell of origin is a fetal liver hematopoietic stem or progenitor, not a bone marrow cell.[1-3,30]

Klusmann et al.[30] reported a median age at diagnosis of 3 days, ranging from 0 day to 65 days. Most of the patients presented with hepatosplenomegaly, pleural or pericardial effusions, or ascites. MLL gene rearrangements were the most frequent single abnormality. The estimated 5-year OS and EFS for the whole group were 85 ± 3% and 63 ± 4%, respectively. Presence of additional cytogenetic aberrations was not a marker of adverse prognosis. Multivariate analysis revealed a correlation between high WBC count, ascites, preterm delivery, bleeding diatheses, failure of spontaneous remission and the occurrence of early death.[30]

Although spontaneous resolution is seen in TAM, mortality due to progressive hepatic fibrosis or cardiorespiratory failure is known. High-risk features include conjugated hyperbilirubinemia, hepatomegaly and raised transaminases, high white cell count and cardiorespiratory compromise; megakaryoblasts can infiltrate the pericardial and pleural cavities. Treatment with low-dose cytarabine (0.5–1.5 mg/kg for 5–12 days) has been used with good results. Monitoring is required because some infants with TAM will later develop AML.

## Juvenile Myelomonocytic Leukemia and the Myeloproliferative Disorder of Noonan Syndrome

Juvenile myelomonocytic leukemia is a rare leukemia of early childhood that is associated with genetic abnormalities of the RAS pathway. Median age at presentation is 2 years. Approximately 90% of patients carry either somatic or germ line mutations of PTPN-11, K-RAS, N-RAS, CBL, or NF1 in their leukemic cells. Allogeneic HSCT remains the therapy of choice for most patients with JMML, curing more than 50% of affected children.[31]

A JMML-like condition with spontaneous regression occurs in infants with NS, with the reported incidence as high as 10%, secondary to germline mutations in PTPN11.[32,33] Most cases of NS/MPD resolve spontaneously and progression to AML is exceptional. Fatal progressive disease occurs in 10%. These infants with NS very often also have cardiac anomalies and life-threatening or even fatal complications at least in part caused by leukocytosis and tissue invasion by monocytes, and immature granulocytes may develop in a certain proportion of them. Mild cytoreductive therapy, such as 6-mercaptopurine is recommended.[31]

## CONCLUSION

Supportive care measures including hydration, prophylaxis for tumor lysis, antibiotics and transfusion support are important in managing neonates with leukemia. Cytoreduction might be warranted for symptomatic leukostasis as well as large organomegaly interfering with vital functions. Recognition of TAM in DS and NS/MPD is important for prognostication. Despite the current guarded prognosis for several variants of neonatal leukemia, high-intensity multiagent chemotherapy with HSCT can cure a proportion of these patients.

## KEY POINTS

- Neonatal leukemia accounts for less than 1% of all childhood leukemia with incidence of 1–5 cases per million live births
- Neonatal leukemia can present with antenatal hydrops and stillbirth
- Presentation with cutaneous skin nodules (leukemia cutis or the "blueberry muffin" appearance) is characteristic in neonates
- Hepatosplenomegaly, lack of lymphadenopathy, involvement of CNS and extramedullary involvement including the lungs are important clinical features
- AML, M4 and M5 subtypes are common and present with high counts, extramedullary disease and MLL rearrangements. Treatment is based on anthracyclines and cytarabine. OS is 30%
- Acute megakaryoblastic leukemia (M7) without associated DS is characterized by t(1;22); osteolysis, liver, and marrow fibrosis might have better outcome in the presence of this translocation
- Neonatal ALL is characterized by a CD10 negative pro-B immunophenotype, high total counts and MLL rearrangement
- TAM in DS secondary to GATA1 mutations is usually self-limiting and has excellent outcomes. However, low-dose cytarabine therapy may be needed
- Neonates with the NS develop a self-limiting MPD resembling JMML secondary to mutations in PTPN11 in the RAS pathway.

## REFERENCES

1. Orbach D, Sarnacki S, Brisse HJ, Gauthier-Villars M, Jarreau PH, Tsatsaris V, et al. Neonatal cancer. Lancet Oncol. 2013;14(13):e609-20.
2. Sande JE, Arceci RJ, Lampkin BC. Congenital and neonatal leukemia. Semin Perinatol. 1999;23(4):274-85.
3. Isaacs H Jr. Fetal and neonatal leukemia. J Pediatr Hematol Oncol. 2003;25(5):348-61.
4. Resnik KS, Brod BB. Leukemia cutis in congenital leukemia. Analysis and review of the world literature with report of an additional case. Arch Dermatol. 1993;129(10):1301-6.
5. Bresters D, Reus AC, Veerman AJ, van Wering ER, van der Does-van den Berg A, Kaspers GJ. Congenital leukaemia: the Dutch experience and review of the literature. Br J Haematol. 2002;117(3):513-24.
6. Reaman G, Zeltzer P, Bleyer WA, Amendola B, Level C, Sather H, et al. Acute lymphoblastic leukemia in infants less than one year of age: a cumulative experience of the Children's Cancer Study Group. J Clin Oncol. 1985;3(11):1513-21.
7. Bajwa RP, Skinner R, Windebank KP, Reid MM. Demographic study of leukaemia presenting within the first 3 months of

life in the Northern Health Region of England. J Clin Pathol. 2004;57(2):186-8.

8. van der Linden MH, Creemers S, Pieters R. Diagnosis and management of neonatal leukaemia. Semin Fetal Neonatal Med. 2012;17(4):192-5.

9. Mathur NB, Joshi N, Singh T, Singh M. Congenital acute megakaryocytic leukemia. Indian J Med Paediatr Oncol. 2011;32(3):165-7.

10. Shah MD, Sane SY, Mehta BC, Desai MS, Punjawani D, Gundewar VD, et al. Congenital leukemia (a case report). J Postgrad Med. 1984;30(4):247-9.

11. Narayan S, Sharma S, Chandra J, Kulshreshtha R. Clinico-hematological profile of congenital leukemia. Indian J Pediatr. 2004;71(10):927-8.

12. Raj A, Talukdar S, Das S, Gogoi PK, Das D, Bhattacharya J. Congenital leukemia. Indian J Hematol Blood Transfus. 2014;30(Suppl 1):159-61.

13. Dasgupta MK, Nayek N. Congenital leukemia cutis. Indian Pediatr. 2001;38(11):1315.

14. Hjalgrim LL, Westergaard T, Rostgaard K, Schmiegelow K, Melbye M, Hjalgrim H, et al. Birth weight as a risk factor for childhood leukemia: a meta-analysis of 18 epidemiologic studies. Am J Epidemiol. 2003;158(8):724-35.

15. Marcotte EL, Thomopoulos TP, Infante-Rivard C, Clavel J, Petridou ET, Schüz J, et al. Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). Lancet Haematol. 2016;3(4):e176-85.

16. Ross JA. Dietary flavonoids and the MLL gene: A pathway to infant leukemia? Proc Natl Acad Sci USA. 2000;97(9):4411-3.

17. Spector LG, Davies SM, Robison LL, Hilden JM, Roesler M, Ross JA. Birth characteristics, maternal reproductive history, and the risk of infant leukemia: a report from the Children's Oncology Group. Cancer Epidemiol Biomarkers Prev. 2007;16(1):128-34.

18. Slany RK. The molecular biology of mixed lineage leukemia. Haematologica. 2009;94(7):984-93.

19. de Boer J, Walf-Vorderwülbecke V, Williams O. In focus: MLL-rearranged leukemia. Leukemia. 2013;27(6):1224-8.

20. Balgobind BV, Zwaan CM, Pieters R, Van den Heuvel-Eibrink MM. The heterogeneity of pediatric MLL-rearranged acute myeloid leukemia. Leukemia. 2011;25(8):1239-48.

21. Puumala SE, Ross JA, Olshan AF, Robison LL, Smith FO, Spector LG. Reproductive history, infertility treatment, and the risk of acute leukemia in children with Down syndrome: a report from the Children's Oncology Group. Cancer. 2007;110(9):2067-74.

22. Choong K, Freedman MH, Chitayat D, Kelly EN, Taylor G, Zipursky A. Juvenile myelomonocytic leukemia and Noonan syndrome. J Pediatr Hematol Oncol. 1999;2(6)1:523-7.

23. Gray ES, Balch NJ, Kohler H, Thompson WD, Simpson JG. Congenital leukaemia: an unusual cause of stillbirth. Arch Dis Child. 1986;61(10):1001-6.

24. Kawasaki Y, Makimoto M, Nomura K, Hoshino A, Hamashima T, Hiwatari M, et al. Neonatal acute megakaryoblastic leukemia mimicking congenital neuroblastoma. Clin Case Rep. 2015;3(3):145-9.

25. Daifu T, Kato I, Kozuki K, Umeda K, Hiramatsu H, Watanabe K, et al. The clinical utility of genetic testing for t(8;16)(p11;p13) in congenital acute myeloid leukemia. J Pediatr Hematol Oncol. 2014;36(5):e325-7.

26. Coenen EA, Zwaan CM, Reinhardt D, Harrison CJ, Haas OA, de Haas V, et al. Pediatric acute myeloid leukemia with t(8;16)(p11;p13), a distinct clinical and biological entity: a collaborative study by the International-Berlin-Frankfurt-Munster AML-study group. Blood. 2013;122(15):2704-13.

27. van der Linden MH, Valsecchi MG, De Lorenzo P, Möricke A, Janka G, Leblanc TM, et al. Outcome of congenital acute lymphoblastic leukemia treated on the Interfant-99 protocol. Blood. 2009;114(18):3764-8.

28. Mann G, Attarbaschi A, Schrappe M, De Lorenzo P, Peters C, Hann I, et al. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study. Blood. 2010;116(15):2644-50.

29. Manola KN. Cytogenetic abnormalities in acute leukaemia of ambiguous lineage: an overview. Br J Haematol. 2013;163(1):24-39.

30. Klusmann JH, Creutzig U, Zimmermann M, Dworzak M, Jorch N, Langebrake C, et al. Treatment and prognostic impact of transient leukemia in neonates with Down syndrome. Blood. 2008;111(6):2991-8.

31. Niemeyer CM. RAS diseases in children. Haematologica. 2014;99(11):1653-62.

32. Roberts AE, Allanson JE, Tartaglia M, Gelb BD. Noonan syndrome. Lancet. 2013;381(9863):333-42.

33. Edwards JJ, Martinelli S, Pannone L, Lo IF, Shi L, Edelmann L, et al. A PTPN11 allele encoding a catalytically impaired SHP2 protein in a patient with a Noonan syndrome phenotype. Am J Med Genet A. 2014;164A(9):2351-5.