Rare Congenital Disorders in Infants: Experience of a Tertiary Health Care Centre.

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Abstract: Background: Congenital malformations represent a significant cause of neonatal morbidity and mortality worldwide. They arise due to complex interactions between genetic, environmental, nutritional, and infectious factors, often making the exact etiology difficult to determine. **Case Presentation:** This case series aims to highlight the spectrum, prevalence, and clinical presentation of congenital malformations during infancy, emphasizing the importance of early detection and timely management. We are reporting four rare congenital malformations including some life-threatening entities, presented to a tertiary health care centre of northern India over a period of six months. We included Congenital Pulmonary Airway Malformation, Congenital Dyserythropoetic Anemia-Type II, Cornelia deLange Syndrome, and Down's syndrome with Acute Myelogenous Leukemia. Detailed clinical examination, laboratory investigations, relevant imaging, and other essential investigations were performed to identify and classify congenital anomalies. **Conclusion:** Comprehensive antenatal screening, maternal health education, and improved neonatal care are essential to reduce their burden. Strengthening surveillance and early intervention strategies can play a pivotal role in improving survival and quality of life for affected infants.

Keywords: Airway malformation, anemia, syndrome, leukemia, neonatal morbidity, early diagnosis.

Introduction:

Congenital disorders are structural or functional abnormalities present at birth, although they may present later. The 2021 'Global burden of disease' data revealed that approximately 31.64 million children (0- 14 years) are affected with congenital birth defects worldwide with a 6.68% increase since 1990. Also, the mortality rate has declined from 51.91 (1990) to 23.65 (2021) per lac population with low socio-demographic countries having the highest burden (43.33 per lac) [1]. In India, the birth prevalence of congenital anomalies varies between 184.48 to 230.51 per 10,000 births. Congenital anomalies were found to be the fourth largest cause of neonatal as well as child death (1- 59 months of age). The proportion of congenital anomaly mortality among all causes of mortality had increased from 4.0% in 1990 to 7.9% in 2017, which could be because of reduction in mortality from other major causes of mortality [2].

Congenital heart defects, neural tube defects, Down syndrome, and hemolytic anemias are among the most common entities [3]. They may result secondary to genetic mutations, congenital infections, nutritional deficiencies, environmental insults or could be multifactorial in origin [4]. Identification of a particular disorder with the help of careful clinical examination with or without investigations and appropriate management are the cornerstones to bring down the associated morbidity and mortality.

Methodology:

This case series aimed to highlight the importance of early recognition, appropriate interventions, and genetic counseling of parents to reduce the disease burden. We included four cases of different congenital disorders presenting to a tertiary health care center of Guru gram over a period of six months (October 2024- March 2025). The criteria for selection were either presentation with life-threatening condition or the rarity of a particular case. Written informed consent was taken from the parents before inclusion and care has been taken to not to disclose identity of any patient.

Case 1:

A full-term (38weeks) female baby (3170 g) was delivered by emergency lower segment cesarean section (LSCS)in view of fetal distress. The 35-year-old primigravida mother was an unbooked case, with no history of any chronic illness or consanguinity and the antenatal period was uneventful. Family history was also insignificant. Baby cried immediately after birth (APGAR: 8, 9), but developed respiratory distress (RDscore 5/10) and shifted to the neonatal intensive care unit (NICU). Cord blood gas showed respiratory acidosis (pH 7.17, pCO_2 60, HCO_3 16.8, BE -6.6, lactate 5.6).

In NICU, baby was managed with non-invasive mechanical ventilation (NIMV) (PIP 18 mmHg, PEEP 6 mmHg, FiO_2 30%) support minimal enteral nutrition (MEN) and first line intravenous antibiotics. Sepsis screening was negative, but chest x-ray (CXR) revealed a large cystic lesion in the left upper-middle lung zone with mediastinal shift to opposite side suggestive of congenital pulmonary airway malformation (CPAM) **(Figure: 1A)**.Chest CT showed a large multiloculated cystic lesion in the left upper lobe, mainly the lingular segments, measuring 3.9 × 3.9 × 2.4 cm **(Figure:1B)**.Ultrasound of the abdomen and cranium and 2D echocardiography ruled out any other associated anomaly. The baby was transferred to a pediatric surgical center, where a left upper lobectomy was performed. Histopathology revealed the presence of multiple dilated cysts lined by ciliated cuboidal to stratified columnar epithelium with interspersed alveolar spaces and confirmed the diagnosis of CPAM-type 2. Baby recovered well after surgery and discharged after 10 days of hospital stay. On follow-up visits baby was thriving well and remained asymptomatic. Follow-up chest X-ray revealed regrowth of remaining lung tissue.

Discussion:

CPAM or congenital cystic adenomatoid malformation (CCAM) is a rare developmental disorder of lung with an incidence of 1:10,000 to 1 in 35,000 live births. It accounts for 95% of all congenital lung cysts while 25% of all congenital lung lesions [5]. There are no associated genetic factors and no correlation with race, gender, or age [6].Uncontrolled growth of terminal bronchioles, abnormal patterning, and dysregulated branching during organogenesis lead to development of such hamartomatous lesion. This dysplastic lesion is commonly unilateral and involves the lower lobe of affected lung [7].In our case, it involved the left upper lobe specifically the lingular segments while Pradheep et al and Badour et al reported similar cases involving left lower lobe [7-8].

Patients may present either in neonatal age with respiratory distress or in pediatric age with recurrent lower respiratory tract infections, depending upon the size of the defect. Rarely, it can present with hemopneumothorax, hemoptysis, or chronic cough [9]. In our case, a female newborn presented with respiratory distress at birth. Pal M et al reported three cases of CCAM presenting with severe respiratory distress at age one month, five months and eight months. One of them was found to have pneumothorax [1]). Pradheep et al reported five-day old neonate with severe respiratory distress and pneumothorax [7].

Radiological investigations including CXR, CT scan, MRI, antenatal ultrasonography, and histopathology of resected lung segment can confirm the diagnosis [11-12]. In our case, CXR and CT chest were both suggestive of the diagnosis of CCAM which was later confirmed by the biopsy report of resected lung segment. Mehta et al reported 15 cases of CCAM, out of which, 8 cases were having rightsided(4 right upper lobe,3 right lower lobe,1 right middle lobe),6casesofleftsided(2 left upper lobe,4 left lower lobe),and1caseofbilateralCCAM[9].

Stocker et al classified CPAM histopathologically into five types as described in**Table 1**[13]. In our case, histopathology confirmed presence of type 2 CCAM. Pal M et al reported three cases of CCAM, out of them two were type 1 while one case was type 2 CCAM [10]. In a study by Mehta et al 15% cases of type 1, 7.8% each of type 2 and 3, 23% type 4 while 38% cases of intermediate type of CCAM have been reported[9].

Surgical excision of the affected segment or entire lobe is the treatment of choice. In our case, patient managed with left upper lobectomy. Mehta et al also reported the 13 patients out of total 15 have undergone surgical excision[9]. Prognosis depends upon type of lesion and macrocystic (>0.5 cm) lesions carry better prognosis. Malignant transformations have also been reported, although rare [14].

Case 2:

A 6-month-old male infant presented with complaints of progressively increasing pallor and poor weight gain for one month. There was no history of previous hospitalization or blood transfusion. Birth history revealed that he was a late preterm

(36 weeks) vaginally delivered neonate and suffered with early-onset neonatal sepsis, requiring 10-day NICU stay. There was no history of consanguinity or any chronic maternal illness. Baby was on exclusive breastfeeding, received primary vaccination and developmentally normal for age. Family history was also insignificant. At the time of admission, the infant was having heart rate- 122/min, RR 54/min, CFT <3 sec and severe pallor with no dysmorphic features. Examination revealed severe malnutrition (< 3rd percentile) and hepatosplenomegaly. Baseline investigations including complete blood counts (CBC), peripheral smear, and liver function testswere sent as listed in **Table 2**. The results were suggestive of hemolytic anemia. The causes for hemolytic anemia were ruled out with negative direct coomb's test (DCT), negative osmotic fragility test, and normal high performance liquid chromatography (HPLC) (HbA2: 3.2%). Serum ferritin levels werehigh (847 ng/ml). Bone marrow examination revealed binucleated erythroblasts (>10%) with variable size nuclear lobes, karyorrhexis, and reversed M:E ratio **(Figure 2B)** suggestive of type 2 congenital dyserythropoetic anemia (CDA). Genetic tests could not be done because of financial issues. Patient received conservative management including blood transfusions, chelation therapy, and nutritional rehabilitation. Patient is under regular follow-up withmonitoring of hemoglobin levels and serum ferritin levels. The growth percentiles improved from below 3rd percentile to just above 10th percentile on follow-up visit.

Discussion:

CDA is a group of rare hereditary hemolytic anemiasthat has been mainly reported in Europe (0.24- 0.71 cases per million) and very rarely reported in Indian subcontinent [15]. It is characterized by ineffective erythropoies is leading to cytopenia of single cell lineage. Classically it is categorized into three subtypes I, II, and III. Type II is the most common form of CDA and is an autosomal recessive disorder affecting SEC23 gene. This gene encodes cytoplasmic coat protein II (CCP II), involved in trafficking of intracellular vesicles [16]. The age of presentation and clinical picture is variable. Patients may present in neonatal period with indirect hyperbilirubinemia (62%) or in older age group with anemia, jaundice, or splenomegaly [17]. Our case presented at six months of age with anemia, hepatosplenomegaly, and growth retardation. In an Indian study by Dass et al, most of the patients presented during early childhood to adolescent age group [15].

Type IICDA is characterized by presence of normocytic anemia, anisopoikilocytosis, and basophilic stippling with normal or raised reticulocyte counts [18]. Presence of erythroid hyperplasia with binucleated erythroblasts (>10%), along with presence of karyorrhexis are the distinctive bone marrow findings [19]. Our case was having severe dimorphic anemia, anisopoikilocytosis, reticulocytosis, with thrombocytopenia and bone marrow examination revealed erythroid hyperplasia along with presence of >10% variable size binucleated erythroblasts and karyorrhexis. The presence of dimorphic anemia can be explained by co-existence of nutritional deficiencies. Sharma et al also

reported bicytopenia, anisopoikilocytosis, and reticulocytosis with bone marrow showing dyserythropoesis and binuclearity suggestive of type II CDA [20].
Complications include splenomegaly, hypersplenism, cholelithiasis, and iron overload [15]. Iron overload secondary to ineffective erythropoiesis, is the most common complication, even in non-transfusion dependent patients and may lead to liver disorders, cardiac problems, and endocrinal problems [21]. Management includes blood transfusion with chelation therapy for iron overload, which should be considered as serum ferritin exceeds 800- 1000 ng/ml or LIC more than 3- 5 mg/gram of dry weight [22]. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment option, although, gene therapy trials are underway [17].
Type I is an autosomal recessive while type III is autosomal dominant disorder. Type I is characterized by moderate to severe anemia and congenital anomalies of the skeletal system [23]. On light microscopy, Type I is characterized by presence of internuclear chromatin and cytoplasmic bridges in binucleated erythroblasts and type III by presence of giant multinucleated erythroblasts. On electron microscopy, "Swiss cheese" nuclei are found in type I while type III shows presence of autophagy vacuoles and myelin figures in cytosol of erythroblasts [24]. Ray et al reported two cases of type I CDA from India, having dyserythropoiesis, karyorrhexis, and inter-chromatin bridges on bone marrow examination [25].

Case 3:

A full-term (38+2 weeks) male infantwas delivered vaginally to a second gravida unbooked mother. She had no documented antenatal visits with no antenatal scans. She had no history of any chronic illness, medication use, radiation exposure, or substance abuse. Her first child is a 3 years old healthy full-term female.The baby cried immediately after birth (APGAR: 8,9), but developed respiratory distress (RD score 4/10) and was shifted to the NICU. Baby diagnosed with transient tachypnea of newborn (TTNB) and improved in next 12 hours. Distinctive facial dysmorphic features were noted including synophrys (2), short nose (2), long philtrum (2), thinner upper lip (2), microcephaly (1), smaller hands (1), hairy body (1), low-set ears, long eyelashes, and low anterior hairline(**Figure 3**). The baby was also small for gestational age (SGA) (1) with birth weight of 2165 grams. Additional findings were small nipples, left undescended testis, and micropenis. The dysmorphic features fulfilled the 'International consensus statement criteria' for Cornelia de Lange syndrome (CdLS).
Ultrasound cranium and whole abdomen showed no congenital anomalies, except the left testis located in the left inguinal canal. Two-dimensional echocardiography revealed a moderate-sized (6 mm) ostium secundum ASD. Parents refused genetic testing due to financial constraints. On follow-up visits, baby was healthy and thriving well with mild hypotonia anddelayed milestones, for which occupational therapy has been advised.

Discussion:

Cornelia de Lange syndrome (CdLS), was named after a Dutch pediatrician Cornelia de Lange (1933), with a prevalence of 1 in 10,000-30,000. In 2018, the first international consensus statement was given by Kline et al regarding the diagnosis and management of this rare entity [26]. This genetic disorder results due to mutations involving one of the seven known genes (NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8 and ANKRD11) affecting the 'Cohesin' complex [27]. The 'Cohesin' complex (composed of a central ring and a regulatory chain) is a multifunctional complex involved in various processes including gene expression [28].

Sporadic cases are more common with more than 99% classic CdLS having heterozygous NIPBL gene mutation, although it can propagate as autosomal dominant or X-linked in heritance [27]. The characteristic phenotype consists of distinctive cranio-facial features, growth retardation, intellectual disability, and limb reductions. Additional abnormalities like gastro-oesophageal reflux (GER) (most common: 93.3%), congenital heart diseases (~30%), hearing loss (80%), renal (10%), and genital involvement (50- 75%) can also be present(29). Diagnosis is based more on clinical features than genetic testing. The spectrum includes classic and non-classic variants and have been defined by the International CdLS consensus group **(Table 3)**[26]. Patients meeting ≥ 11 points with at-least 3 cardinal features do not need any genetic testing and termed as classic CdLS while patients meeting 9-10 points with at-least 2 cardinal features are termed as non-classic CdLS. Patients with 4-8 points needs to be tested genetically before being labelled as CdLS while patients with <4 points are excluded from CdLS spectrum [26].

The above case has fulfilled the criteria for classic type of CdLS (Total score 12), although we have advised genetic testing but parents denied due to financial reasons. Reddy et al and Meshram et al also consecutively reported a 5-year-old and a 4-year-old case of classic CdLS [30-31]. In contrast, Savitha et al reported a case of 18 months old non-classic CdLS with positive RAD21 mutation [32]. Mutation analysis like panel sequencing, sanger sequencing,and whole exome sequencing (WES) are the cornerstones. A multidisciplinary approach is required for management of associated morbidities including occupational therapy and speech/ language therapy. Management of GER, hearing aids, growth and nutritional rehabilitation, medical and surgical management of genitourinary abnormalities are the measures to improve the quality of life [33].

Case 4:

A late preterm male baby (36+4 weeks, 2500 g) was delivered vaginally to a 35 years unbooked mother.The mother had an uneventful antenatal period with no history of any chronic illness or consanguinity, although no antenatal ultrasounds were available. Past obstetric history was suggestive of a four years old healthy female child and one

spontaneous abortion 3 years back. This baby had an uneventful postnatal course (APGAR: 8,8) and examination revealed stable vitals but dysmorphic features, including upward-slanting palpebral fissures, almond-shaped eyes, low-set ears, bilateral foot saddle gaps, and mild hypotonia on neurological assessment. Parents were counseled for the possibility of a congenital disorder and need for further investigations but they left against medical advice (LAMA) on second day of life.

On 5thday of life, the infant returned to the emergency department with lethargy, poor feeding, and jaundice, the examination findings were HR 148/min, RR 52/min, CFT<3 seconds, BP 72/38 mmHg (mean 49), SpO_2 97% on room air,and mild hepatosplenomegaly. Sepsis screen and CSF analysis were suggestive of meningitis; henceintravenous antibiotics were started.Karyotyping was also sent after parental consent. 2D echocardiography revealed ostium secundum atrial septal defect (ASD).Baby showed initial improvement but repeat investigations revealed persistently elevated CRP (56 mg/L), markedly raised total leukocyte count (53,390/cmm), severe thrombocytopenia (35,000/cmm), and presence of atypical cells(74% blast cells, 12% neutrophils, 8% monocytes, 6% lymphocytes) in peripheral smear. A provisional diagnosis of acute myeloid leukemia (AML) was made, and later confirmed by bone marrow examination which revealed presence of blasts of myeloid lineage with positive cytochemical myeloperoxidase (MPO) staining. A diagnosis of acute myeloid leukemia with monocytoid cells was made, although confirmatory tests like flow cytometry could not be done because of financial constraints. Karyotyping confirmed Down syndrome (Trisomy 21; 47, XX). Meanwhile, patient's condition deteriorated and baby could not survive despite best efforts.

Discussion:

Congenital leukemia (CL) is a rare entity with an incidence of 1- 5 per million live births. It accounts for less than 1% of total childhood leukemia and usually presents within first 28 days of life. In contrast to childhood leukemia, its origin from myeloid series leads to acute myeloid leukemia (AML) in 50- 60% of cases with poor prognosis and high mortality rate (~ 70% within two years) [34]. The criteria being used for the diagnosis includes: 1) presentation within 4 weeks of life; 2) proliferation of immature myeloid, lymphoid, or erythroid series; 3) infiltration of non-hematopoietic tissues; and 4) absence of other diseases [35]. Congenital infections, intrauterine environmental insults, radiation exposure, andchromosomal abbreviations like Down's syndrome, Turner syndrome, Klippel Feil syndrome, and Ellis van Crevald syndrome are the common associations with CL. A fourfold higher incidence of AML in DS children has been reported by the Children's Oncology Group [36]. Our case was having typical facial features of DS which was confirmed by karyotyping.

Down syndrome (DS) or Trisomy 21 is the most common cytogenetic abnormality seen with a rate of 1:700 to 1:1000 live births. Children with DS have significantly higher risk of leukemia with transient myeloproliferative disorder (TMD) and acute myelogenous

leukemia (AML) being the two most common entities [37]. Presence of blast cells involving myeloid series in bone marrow, lineage specific staining, and flow cytometry are the cornerstones for diagnosis of both the entities. Down's syndrome associated TMD and AML; both are indistinguishable clinically as well as morphologically. TMD is carrying a good prognosis with spontaneous remission while AML carries a grave prognosis with progressive deterioration and complications [37].

In our case bone marrow revealed the presence of acute myeloid leukemia with immature monocytoid cells. Further, work-up could not be done because of financial constraints of parents. Before considering other arrangements to help the family, unfortunately, the patient got deteriorated clinically and could not survive. Raj A et al reported a case of preterm (33 weeks; 1600 grams) neonate having Down's syndrome. Baby remained asymptomatic while the blood investigations revealed presence of blast cells, later confirmed by immunophenotyping. Baby died because of unexplained complications [38]. Gosavi et al reported two cases of Down's syndrome with TMD, diagnosed by peripheral smear with negative cytochemical staining. They found spontaneous remission of peripheral smear findings in both the cases. One baby died while other survived and was growing well [39].Bagri et al reported a case of full-term neonate with Down's syndrome and AML. Neonate had respiratory distress and diagnosed with karyotyping (Trisomy 21), peripheral blood smear (40% blasts), and flow cytometry (megakaryocytic differentiation) [40].

The present case emphasizes that neonates with Down's syndrome should be actively screened for hematological disorders by detailed blood picture. Any deviation from normality warrants further work-up and appropriate management. Congenital leukemias carry worse prognosis with high mortality rates, hence should be sought promptly.

Limitations:

Our institute is a private medical college, serving the rural population of Haryana. Hence, facing an issue of financial instability of the patients. Some of the investigations required for confirmatory diagnosis of a particular disease, carries high cost and becomes a limitation. This study is also suffered with this limitation.

Conclusion:

Congenital disorders continue to pose challenges due to their complex and multi factorial origins. This case series highlighted the importance of careful clinical examination, timely interventions, and appropriate management, with which even the rarest of the diseases can be managed successfully. With the advancement of modern medicine, the life-threatening complications can be treated effectively medically or surgically. Three out of four above mentioned cases are thriving well, although we lost one child. This further prompts the clinicians to have focused approach and spread awareness about these rare entities.

References:

1) Peykari N, Khalili D, Mohammadi S, Kasaeian A, Naghavi M. Trend of mortality due to congenital anomalies in children younger than 5 years in Iran: Findings from the Global Burden of Disease study 1990–2019. BMC Pediatr. 2024; 24:62.
2) Li Y, He C, Yu H, Wu D, Liu L, Zhang X. Global, regional, and national epidemiology of congenital birth defects in children from 1990 to 2021: a cross-sectional study. BMC Pregnancy Childbirth. 2025 Apr 24; 25(1):484.
3) Christianson A, Howson CP, Modell B. March of Dimes: Global Report on Birth Defects. White Plains (NY): March of Dimes Birth Defects Foundation; 2006.
4) Wu D, Xu J, Liu J, Liu X, Xu X, Zhou Y, et al. Congenital anomalies: epidemiological, clinical, and management aspects in low- and middle-income countries. Front Pediatr. 2023; 11:1165081.
5) Walvir, Nazia Manzoor1; Makhdoomi, Rumana1; Abeer, Inara1; Ganaie, Farooq2; Maqsood, Shadab3. A complete spectrum of congenital cystic adenomatoid malformation of the lung deceptive clinical presentations and histological surprises; a single institutional study from a tertiary care hospital in North India. Lung India 40(5):p 423-428, Sep–Oct 2023.
6) Nur S, Badr R, Sandoval C, Brudniki A, Yeh A. Syndromic presentation of a pleuropulmonary blastoma associated with congenital cystic adenomatoid malformation: a case report. J Pediatr Surg. 2007;42:1772-77.
7) Pradheep RR, Devadas S. Type 1 Congenital Pulmonary Airway Malformation (CPAM): A Case Report. Indian Journal of Neonatal Medicine and Research. 2019, Jan, Vol-7(1): PC01-PC03.
8) Badour M, Hussain B, Hammed A, Sawssan Ali, Falyon S. A rare case of congenital cystic adenomatoid malformation: Mimics pneumonia manifestations. Ann Med Surg (Lond). 2021 May 27;66:102433.
9) Mehta AA, Viswanathan N, Vasudevan AK, Paulose R, Abraham M. Congenital Cystic Adenomatoid Malformation: A Tertiary Care Hospital Experience. J Clin Diagn Res. 2016 Nov;10(11):SC01-SC04.
10) Pal M, Das I, Hazra R, Mukhopadhyay S, Bandyopadhyay S. Congenital cystic adenomatoid malformation of lung: Report of three cases and review of this rare entity. Clin Cancer Investig J 2016;5:466-9.
11) Nadeem M, Elnazir B, Greally P. Congenital pulmonary malformation in children. Scientifica. 2012: 209896.
12) Luján M, Bosque M, Mirapeix RM, Marco MT, Asensio O, Domingo C. Late onset congenital cystic adenomatoid malformation of the lung. Embryology, clinical symptomatology, diagnostic procedures, therapeutic approach and clinical follow up. Respiration. 2002;69(2):148-54.
13) Stocker JT. The respiratory tract. In: Stocker JT, Dehner LP, eds. Pediatric pathology. Philadelphia, PA:Lippincott Williams & Wilkins; 2001. Pp. 445-517.

14) David M, Lamas-Pinheiro R, Henriques-Coelho T, Prenatal and Postnatal management of congenital pulmonary airway malformation, Neonatology. 2016;110:101-115.
15) Dass J, Nayak AR, Puri V, Aggarwal M. Congenital dyserythropoietic anemia in children: Case series with review of literature. PHOJ. 2024;9(2):55-61.
16) Schwarz K, Iolascon A, Verissimo F, et al. Mutations affecting the secretory COPII coat component SEC23B cause congenital dyserythropoietic anemia type II. Nat Genet.2009;41(8):936-940.
17) Akpan IJ, Bogyo K, Leeman-Neill RJ, Wattacheril J and Francis RO. Congenital dyserythropoietic anemia type II and ineffective erythropoiesis: challenges in diagnosis and management. Front. Hematol. 3:1389820.
18) Iolascon A, Esposito MR, Russo R. Clinical aspects and pathogenesis of congenital dyserythropoietic anemias: from morphology to molecular approach. Haematologica. 2012;97(12):1786-1794.
19) Heimpel H, Kellermann K, Neuschwander N, H¨ogel J, Schwarz K. The morphological diagnosis of congenital dyserythropoietic anemia: results of a quantitative analysis of peripheral blood and bone marrow cells. Haematologica. 2010;95(6): 1034-1036.
20) Sharma T, Vaswani S, Barman D, Didel S, Purohit A. Congenital dyserythropoietic anemia type II—A rare case report. Indian J Pathol Microbiol2025;68:435-7
21) Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. Br J Haematol. (2016) 172:512–23.
22) Aydinok Y. Iron chelation therapy as a modality of management. Hematol Oncol Clin North Am. (2018) 32:261–75.
23) Roy NBA, Babbs C. The pathogenesis, diagnosis, and management of CDA type I. Br J Haematol. 2019;185(3):436-449.
24) Achille Iolascon, Immacolata Andolfo, Roberta Russo. Congenital dyserythropoietic anemias. Blood 2020; 136 (11): 1274–1283.
25) Ray S, Saikia D. Congenital dyserythropoietic anemia type I - A Case Report. Iran J Ped Hematol Oncol 2024; 14 (1) :74-77.
26) Kline AD, Moss JF, Selicorni A, Bisgaard AM, Deardorff MA, Gillett PM, et al. Diagnosis and management of Cornelia de Lange syndrome: first international consensus statement. Nat Rev Genet. 2018 Oct;19(10):649-666.
27) Tonkin, E. T., Wang, T. J., Lisgo, S., Bamshad, M. J. & Strachan, T. NIPBL, encoding a homolog of fungal Scc2-type sister chromatid cohesion proteins and fly Nipped-B, is mutated in Cornelia de Lange syndrome. Nat. Genet. 36, 636–641 (2004).
28) Alonso-Gil D, Losada A. NIPBL and cohesin: new take on a classic tale. Trends Cell Biol. 2023;33:860-71.

29) Kline AD, Krantz ID, Sommer A, Kliewer M, Jackson LG, FitzPatrick DR, Levin AV, Selicorni A. Cornelia de Lange syndrome: Clinical review, diagnostic and scoring systems, and anticipatory guidance. Am J Med Genet Part A.2007; 143A:1287–1296.
30) Reddy K,G.A. Manjunath, Pranam U, G.A. Pranam.Cornelia De Lange Syndrome: A Case Report of a 5 Year Old Boy. Pediatr. Res. 2017; 5(1): 41-43.
31) Meshram GG, Kaur N, Hura KS. Cornelia De Lange Syndrome In A 4-Year-Old Child From India: Phenotype Description And Role Of Genetic Counseling. Med Arch. 2018 Oct;72(4):297-299.
32) Savitha MR, Shervani MB. Cornelia de Lange syndrome type 4 with a novel heterozygous missense variant in RAD 21 gene. Int J Contemp Pediatr 2024;11:605-8.
33) Ascasoa A, Arnedob M, Puisacb B, Latorre-Pellicerb A, Rincónc JD, Bueno-Lozanoc G, et al. Cornelia de Lange Spectrum. An. Pediatr. 2024;100: 352-62.
34) Green K, Tandon S, Ahmed M, Toscano W,O'Connor D, AncliffP, et al. Congenital acute myeloid leukemia:challenges and lessons. A 15-year experience from the UK. Leukemia & Lymphoma. 2020; 62(3): 688–695.
35) Bresters DR, Veerman A, Van Wering E, et al. Congenital leukaemia: the Dutch experience and review of the literature. Br J Haematol. 2002;117(3):513–524.
36) Safia R, Zeeba SJ, Sonia G. Congenital leukemia in down's syndrome – A rare case report. Banglad J Med Sci 2012;11:68.
37) Mateos MK, Barbaric D, Byatt SA, Sutton R, Marshall GM. Down syndrome and leukemia: insights into leukemogenesis and translational targets. TranslPediatr 2015;4(2):76-92.
38) Raj A, Talukdar S, Das S, Gogoi PK, Das D, Bhattacharya J. Congenital leukemia. Indian J Hematol Blood Transfus. 2014 Sep;30(Suppl 1):159-61.
39) Gosavi AV, Murarkar PS, Lanjewar DN, Ravikar RV. Transient leukemia in down syndrome: report of two cases with review of literature. Indian J Hematol Blood Transfus. 2011 Sep;27(3):172-6.
40) Bagri DR, Mehta A, Sharma A, Gulati S, Bairwa R, et al. (2024) Congenital B-Cell Acute Myeloid Leukemia Associated with Down's syndrome. J Neonatol Clin Pediatr 11: 124.

Table 1: Histopathological classification of CCAM

Type	Frequency	Origin	Cyst Size	Cyst Lining
0	<3%	Trachea/ major bronchi	No cysts/ cysts <0.5 cm	Pseudostratified ciliated columnar epithelium

1	50- 70%	Distal bronchi/ proximal bronchiole	Large (2-10 cm)	Pseudostratified ciliated columnar epithelium
2	20- 40%	Acinar origin	Intermediate (0.5-2 cm)	Ciliated cuboidal/ columnar epithelium
3	5- 10 %	Acinar origin	Small (<0.5 cm)	Ciliated cuboidal epithelium
4	10- 15%	Alveolar epithelium	Small	Ciliated cuboidal epithelium

Abbreviations: CCAM: Congenital cystic adenomatoid malformation

Table 2: Baseline Investigations of Congenital Dyserythropoetic Anemia Case

Parameters	Results	Peripheral Smear
Hemoglobin	5.0 gm/dl	Reduced RBC count with predominantly microcytic hypochromic picture along with many fragmented cells, helmet cells, schistocytes, tear drop cells, target cells, elliptocytes and few howell jolly bodies, along with reversal of M:E ratio.**Impression:**Leucoerythroblastic picture with dimorphic anemia**(Figure 2A)**
TLC	9,600 cells/cm^3	
DLC	N=37;L=17;M=20; E=04; M=22	
Platelet count	80,000/ mm^3	
Hematocrit	15.0 %	
MCV	60.6 fl	
MCHC	33.3 g/dl	
MCH	20.4 pg	
RDW	40.4	
Reticulocyte counts	7.2%	
Bilirubin (T/D/I)	6.1/ 0.7/ 5.4 mg/dl	

Abbreviations: TLC: total leucocyte count, DLC: differential leucocyte count, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, MCH: mean corpuscular hemoglobin, RDW: red cell distribution width, T/D/I: total/ direct/ indirect, RBC: red blood cell, M:E: myeloid erythroid ratio.

Table 3: Clinical criteria for Cornelia deLange Syndrome

S	Clinical Features	Points

No		
A.	Cardinal Features • Meeting of the medial eyebrows in the midline and/or thick eyebrows • Short nose, concave nasal ridge, and/or nose with an upturned tip • Long and/or smooth philtrum • Thin upper lip and/or downturned corners of mouth • Presence of fewer than the normal number of fingers and/or absence of fingers or toes from birth • Congenital diaphragmatic hernia	2 points each if present
B.	Suggestive features • Global developmental delay and/or intellectual disability/learning disability • Prenatal growth retardation • Postnatal growth retardation • Microcephaly • Small hands and/or feet • Short fifth finger • Abnormally increased hair growth	1 point each if present
Clinical Score • ≥ 11 points, of which at least 3 are cardinal: classic CdLS • 9-10 points, of which at least 2 are cardinal: non-classic CdLS • 4-8 points, of which at least 1 is cardinal: individual should be genetically tested for CdLS • < 4 points: insufficient for genetic testing		

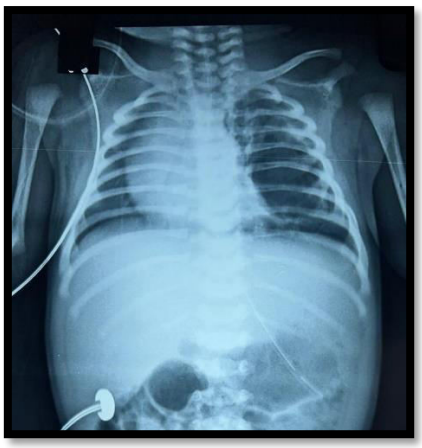

Figure 1A

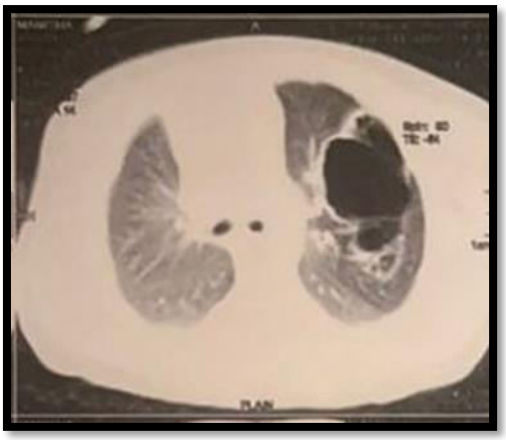

Figure 1B

Figure 1: (A): Chest X-ray showinglarge cystic lesion with absent broncho-vascular markings in left upper-middle zone with mediastinal shift to right side; (B): Chest CT scan showing large multiloculated cystic lesion (3.9 X 3.9 X 2.4 cm) with peripheral septations and irregular walls in upper lobe of left lung.

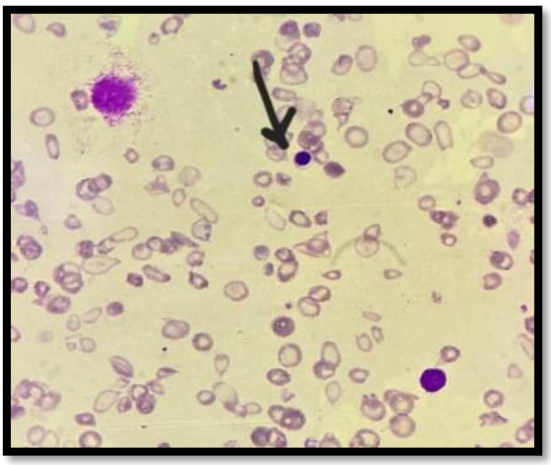

Figure 2A

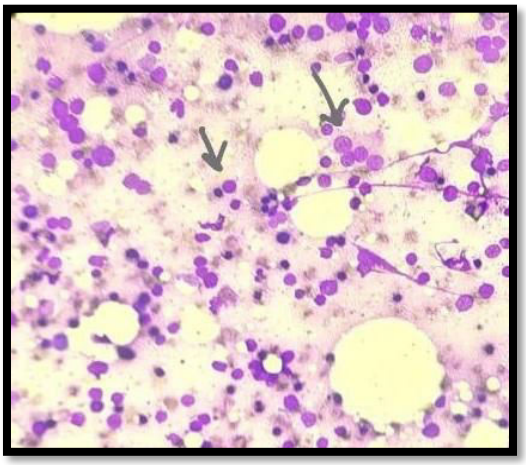

Figure 2B

Figure 2: (A): Peripheral smear showing Leucoerythroblastic picture with dimorphic anemia (M:E ratio reversal); (B): Bone marrow picture showing variable size red cells with karyorrhexis.

Figure 3: Distinctive clinical features suggestive of Cornelia de Lange Syndrome

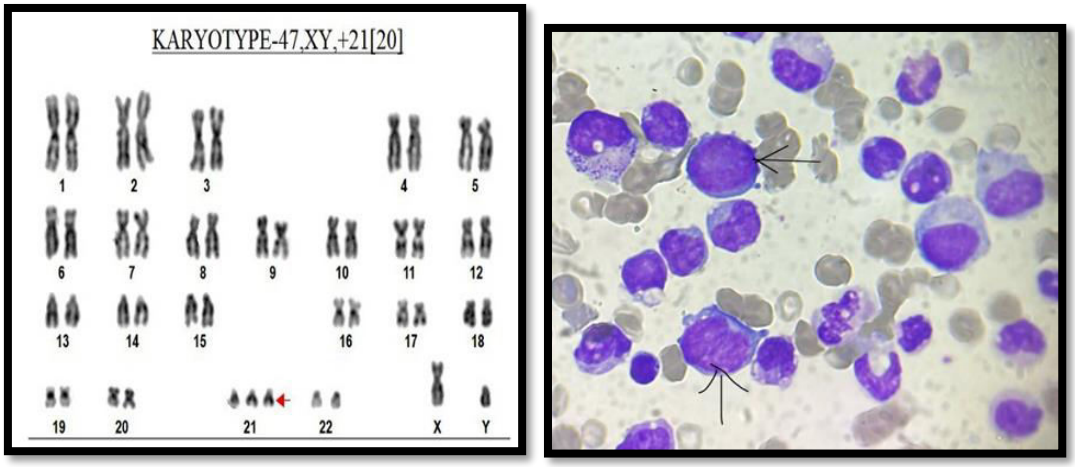

Figure 4A Figure 4B

Figure 4: (A) Karyotyping showing Trisomy 21 (B) Bone marrow smear showing presence of blast cells