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[Case Study] Genetic and Clinical Insights into Congenital Leukemia in a Newborn Conceived via IVF: A Rare Case Study of Congenital Leukemia in One of the Separate Twins

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Abstract

Background: Congenital leukemia is an exceptionally rare condition, with an incidence of 1 to 5 cases per million live births. Despite its rarity, the disease is clinically significant due to its severe manifestations and the need for tailored diagnostic and therapeutic strategies. Clinical features typically include hepatosplenomegaly, thrombocytopenia, and infiltrative cutaneous nodules. Recent advancements have identified the MLL gene as a critical player in leukemogenesis. A thorough understanding of the genetic and clinical aspects of congenital leukemia is essential for optimal patient management and genetic counseling.

Case Presentation: A 1-day-old male newborn, the first child conceived through in vitro fertilization (IVF) for this family, presented with neonatal tachypnea, hepatosplenomegaly, and thrombocytopenia. Genetic analysis revealed a chromosomal translocation involving the MLL gene. His twin brother, conceived simultaneously but developing independently, showed no signs of leukemia. The therapeutic approach included oxygen therapy, platelet transfusions, and supportive care. Follow-up assessments indicated significant improvement in hepatosplenomegaly and hematological indices.

Conclusion: This case highlights the clinical importance of congenital leukemia, particularly in the context of IVF-conceived pregnancies. The observed genetic discordance between the twins suggests the involvement of somatic mutations, chromosomal mosaicism, and epigenetic modifications. Recommendations for reducing the risk of genetic disorders in IVF-conceived pregnancies include preimplantation genetic testing, optimization of culture conditions, parental genetic screening, and ongoing research and education. This case represents the first documented instance worldwide of congenital leukemia occurring in one of the separate twins conceived through in vitro fertilization (IVF).

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1. Introduction

Congenital leukemia in newborns is a rare yet clinically significant challenge in pediatric hematology, manifesting as early-onset leukemia within the neonatal period. Despite its rarity, with an incidence rate ranging from 1 to 5 per million live births, this condition poses unique diagnostic and therapeutic dilemmas due to its complexity. The clinical presentation of neonatal congenital leukemia is varied and often nonspecific, encompassing infiltrative cutaneous nodules, hepatosplenomegaly, thrombocytopenia, and the presence of immature leukocytes in the peripheral blood, complicating accurate diagnosis.[1] Recent advancements in molecular genetics have shed light on the genetic basis of congenital leukemia, highlighting the pivotal role of the MLL (Mixed-Lineage Leukemia) gene. Rearrangements of the MLL gene, resulting from chromosomal translocations, lead to the formation of fusion genes, disrupting normal hematopoietic differentiation processes and contributing to leukemogenesis. [2] In this case, we present a detailed analysis of a 1-day-old male patient diagnosed with congenital leukemia, conceived through in vitro fertilization (IVF), with genetic analysis revealing a chromosomal translocation involving the MLL gene. This case underscores the ongoing research exploring the association between IVF and genetic abnormalities, such as the MLL translocation, aiming to elucidate its genetic basis and implications.

Despite sharing a common intrauterine environment, the twin newborns exhibited discordance in the presentation of congenital leukemia, prompting investigation into potential mechanisms. Possible explanations include stochastic genetic events, differential intrauterine exposures, variations in immune responses, and epigenetic modifications. This study endeavors to document this rare case of neonatal congenital leukemia, investigate its genetic basis, and explore mechanisms of twin discordance. This case underscores the importance of personalized diagnostic and therapeutic strategies in managing congenital leukemia, particularly in the context of genetic abnormalities associated with IVF.

2. Case Presentation

A 1-day-old male newborn, conceived through in vitro fertilization (IVF), presents a rare case of congenital leukemia. The parents experienced 11 years of infertility, and this was their first successful IVF procedure. The mother was 40 years old at the time of the pregnancy. The patient is one of twin males, born at 36 weeks gestation. The other twin is in good health and has been discharged home.

The patient was initially transferred with a diagnosis of neonatal tachypnea (NT) at 36 weeks, admitted 12 days prior with respiratory distress (RD). The patient was intubated and gradually weaned from mechanical ventilation, currently maintained on nasal continuous positive airway pressure (N. CPAP) with PEEP 5, FiO2 50%, and an oxygen saturation of 97%. The clinical course was complicated by hepatosplenomegaly and frequent thrombocytopenia, necessitating multiple platelet transfusions.

Chromosomal analysis was conducted to rule out trisomy 21. Physical examination revealed equal air entry bilaterally with With signs of Respiratory distress or adventitious sounds, normal heart sounds with fair perfusion, a lax and soft abdomen with hepatosplenomegaly, and a central nervous system (CNS) exam indicating no fits and anterior fontanelle at level. [**Figure 1**]

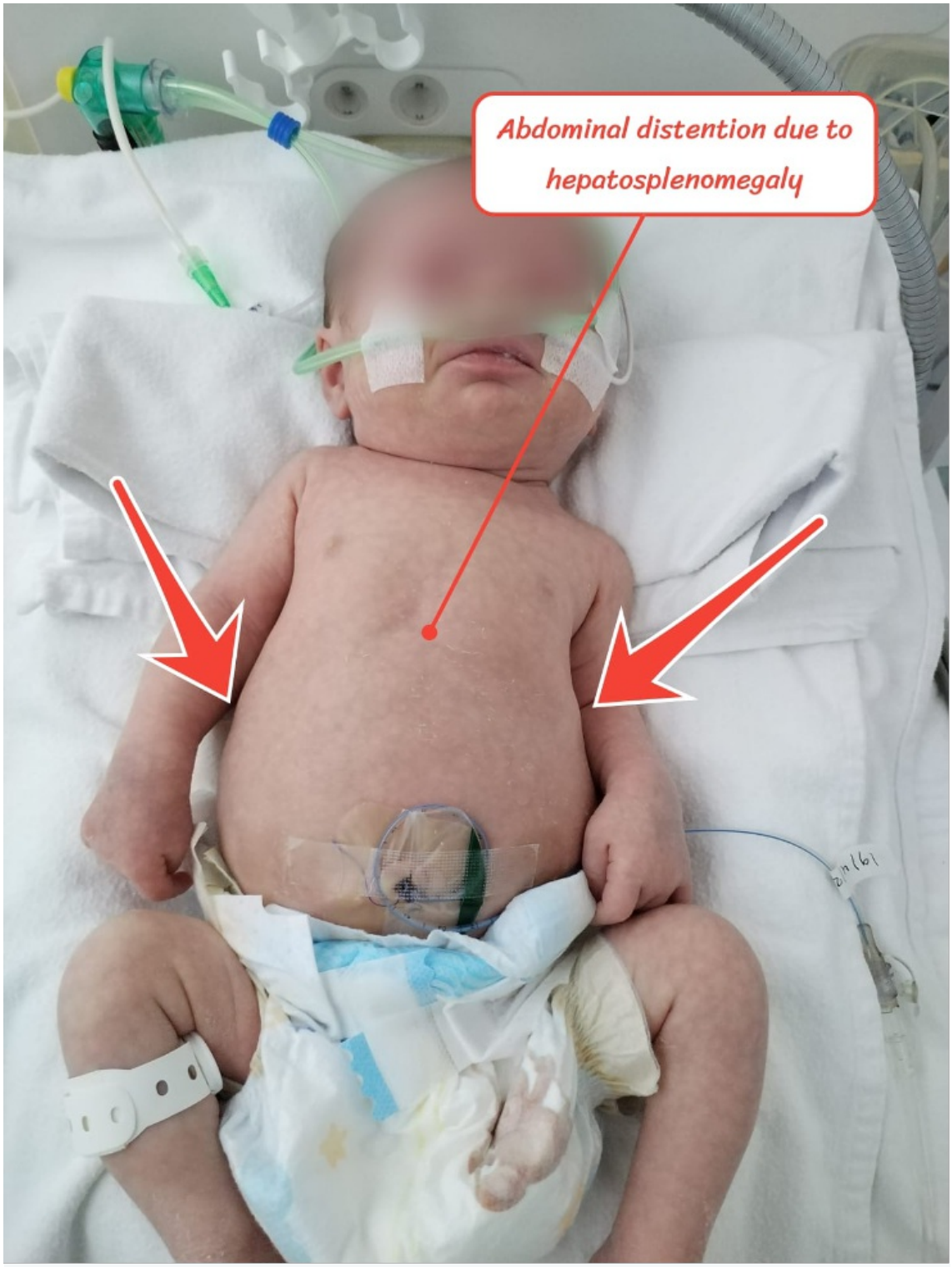

Figure 1. During the physical examination, the patient exhibited equal air entry bilaterally without signs of respiratory distress or adventitious sounds. Cardiac auscultation revealed normal heart sounds with adequate perfusion. Abdominal palpation revealed a lax and soft abdomen, accompanied by hepatosplenomegaly. Additionally, the central nervous system (CNS) examination indicated the absence of seizures, with the anterior fontanelle at an appropriate level. These findings are typical clinical features observed in cases of congenital leukemia.

Laboratory findings showed thrombocytopenia and the presence of blast cells at 10%, with negative C-reactive protein (CRP) and acceptable capillary blood gas (CBG) levels. The patient tolerated nasogastric tube (NGT) feeding of 30 mL

every 3 hours and was on intravenous fluids (IVF), Targocid, and Meropenem. The abdominal ultrasound findings indicated that the liver was mildly enlarged at 8 cm, displaying a homogeneous echo pattern with no focal lesions or dilated intrahepatic biliary radicles. The gall bladder was of average size and wall thickness, with no stones or sludge detected. The common bile duct (CBD) was not dilated. The spleen showed mild splenomegaly at 6.7 cm with no masses. The pancreas was free of masses or duct dilatation. The adrenals were normal, showing no masses or nodules. Both kidneys were in their normal locations, of average size, and regular contour with normal parenchymal thickness and echogenicity, displaying good differentiation between the parenchyma and the collecting system, and were free of stones, backpressure changes, or focal lesions. The gastrointestinal tract showed no dilatation or wall thickening. There was no abdominal or pelvic lymphadenopathy, and no ascites or masses were present in the mesentery, peritoneum, or retroperitoneum. The celiac axis and superior mesenteric artery were patent, as were the portal vein and branches, splenic vein, superior mesenteric vein, and hepatic veins. No abdominal aortic or iliac artery aneurysm was noted. The pelvic ultrasound revealed no masses, ascites, or fluid collections, and the urinary bladder was empty at the time of examination. [**Figure 2**]

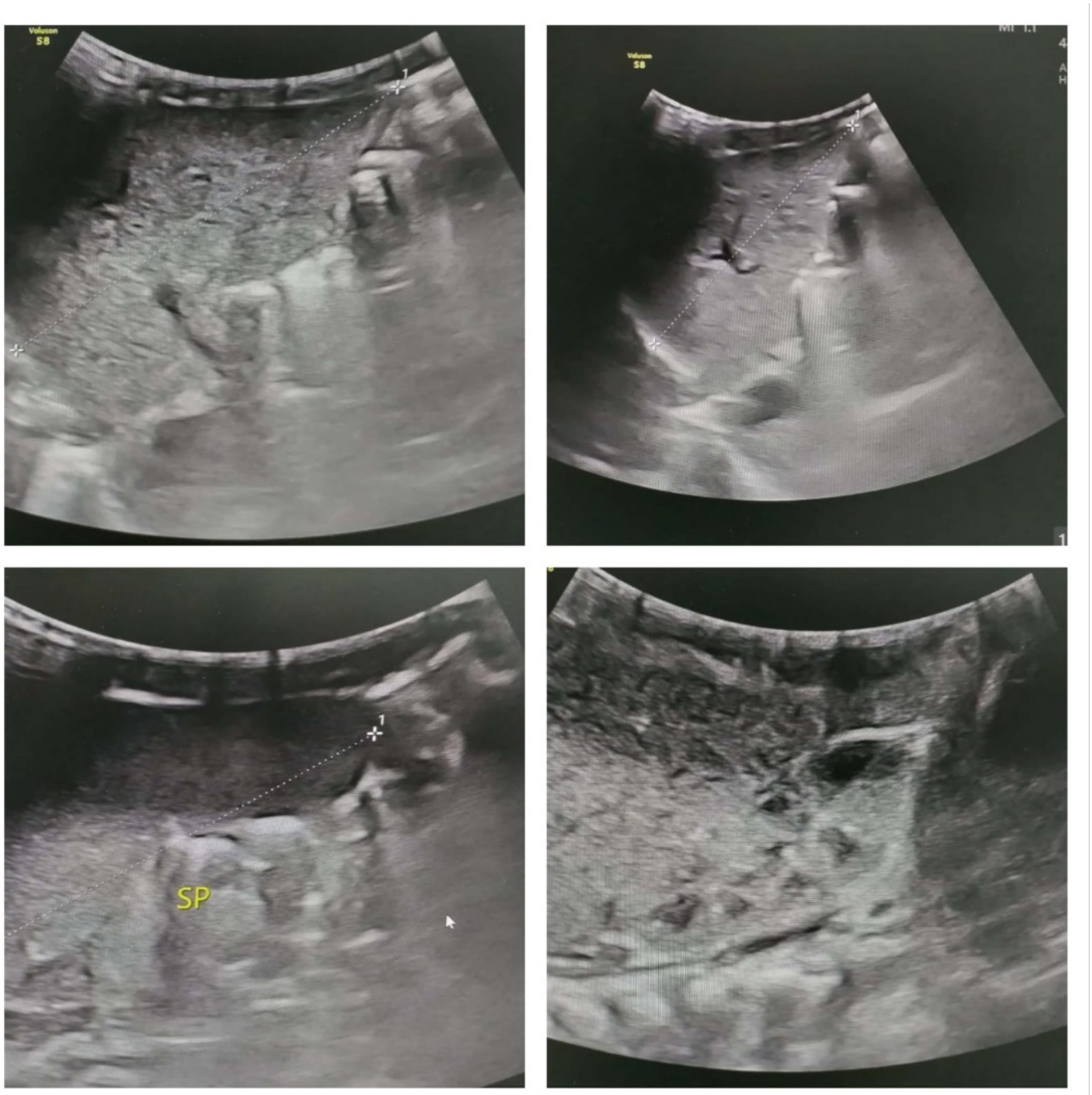

Figure 2. The abdominal ultrasound revealed mild hepatomegaly, with the liver measuring 8 cm in size and displaying a homogeneous echo pattern. Additionally, mild splenomegaly was noted, with the spleen measuring 6.7 cm. The absence of focal lesions or dilated intrahepatic biliary radicles suggests a uniform enlargement of the liver. These findings, along with the presence of hepatosplenomegaly, indicate a systemic condition affecting both organs, consistent with the presentation of congenital leukemia.

The chromosomal analysis report for the patient indicated features suggestive of Down syndrome. The analysis employed standard stimulated blood lymphocyte culture with synchronization, followed by chromosome metaphase slide preparation, GTG staining, and image analysis using CytoVision software. The peripheral blood specimen was deemed adequate, with five cells counted and analyzed, and two cells karyotyped, achieving a band resolution of 550.

The karyotype result was 47, XY,+21, revealing an abnormal male chromosome complement with an extra chromosome

21 (trisomy 21), consistent with the clinical diagnosis of Down syndrome. [3] No additional chromosomal abnormalities were detected within the limits of the current technology. It was recommended that the patient undergo genetic counseling and early intervention to enhance intellectual and physical abilities, as well as prenatal diagnosis for future pregnancies. This test does not exclude the presence of structural chromosomal abnormalities below the resolving power of light microscopy and the banding resolution of the examined metaphase cells. Additionally, it cannot rule out low-level chromosomal mosaicism and other non-chromosomal genetic aberrations. The test was developed, and its performance characteristics were determined following CAP recommendations.

The diagnostic methodology employed in this case involved a comprehensive approach to confirm the diagnosis of congenital leukemia. Initially, the clinical presentation of hepatosplenomegaly, thrombocytopenia, and respiratory distress prompted further investigation. Abdominal ultrasound was conducted to assess the abdominal organs, revealing hepatosplenomegaly and ruling out other intra-abdominal pathologies. Additionally, genetic analysis through chromosomal analysis was crucial in confirming the diagnosis of Down syndrome, which is associated with an increased risk of leukemia. [4]

Furthermore, the hematological assessment, including complete blood count and peripheral blood smear examination, revealed thrombocytopenia and the presence of blast cells, indicative of leukemia. These findings were pivotal in corroborating the clinical suspicion of congenital leukemia. The integration of clinical, radiological, and genetic data played a fundamental role in establishing the diagnosis and guiding further management. **[Figure 3]**

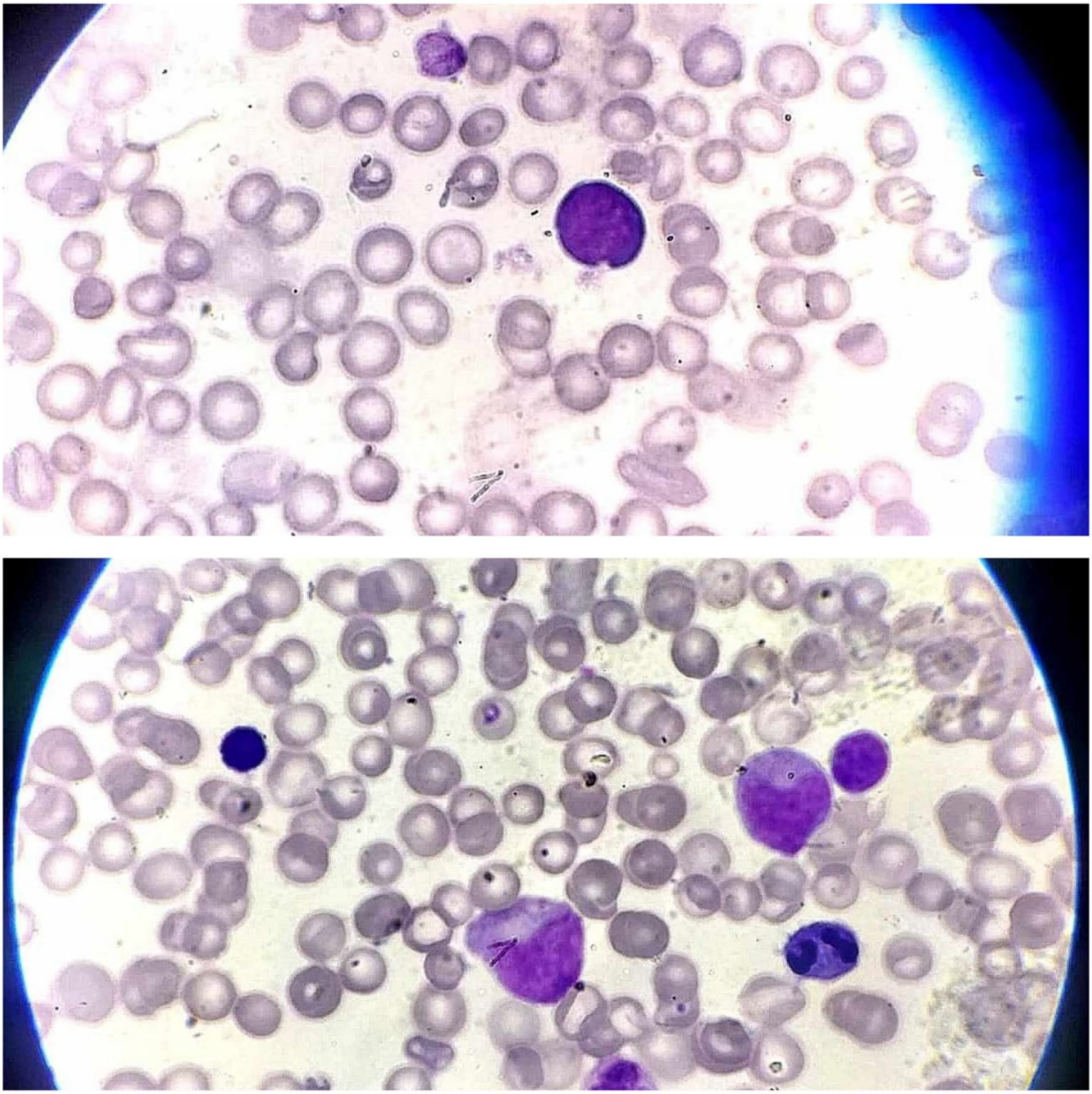

Figure 3. Illustrates peripheral blood smear findings characteristic of congenital leukemia. Notably, the smear reveals the presence of blast cells, which are significantly larger than normal peripheral blood cells and possess prominent nuclei with delicate chromatin and scant cytoplasm. The abundance of these immature leukemic cells is a hallmark of congenital leukemia, underscoring the malignant proliferation of undifferentiated hematopoietic cells. This morphological evidence, in conjunction with clinical findings of hepatosplenomegaly, thrombocytopenia, and respiratory distress, as well as genetic confirmation of Down syndrome, consolidates the diagnosis of congenital leukemia. The meticulous integration of clinical, radiological, and genetic data is critical in the definitive diagnosis and subsequent management of this rare and aggressive neonatal malignancy.

This multidisciplinary approach ensures accurate interpretation and management of this rare form of cancer, allowing clinicians to provide optimal care to affected patients. [5] Immunophenotyping Results: The immunophenotyping results from bone marrow analysis revealed the presence of an abnormal population comprising 5% CD34-positive cells

expressing markers indicative of myeloblasts phenotype. This finding, along with the absence of certain markers and dysplastic features, supported the diagnosis of myeloid leukemia, particularly associated with Down syndrome.[6] The patient's clinical status and morphological features corroborated these immunophenotypic findings, underscoring the importance of integrating laboratory data with clinical assessment for accurate diagnosis and management.

3. Therapeutic Approach

Upon admission to the Neonatal Intensive Care Unit (NICU), the patient's management plan was initiated. The approach encompassed various interventions aimed at addressing the clinical manifestations and underlying pathology associated with congenital leukemia. Firstly, oxygen therapy was initiated using a nasal cannula to ensure adequate oxygenation. Intravenous fluids were administered to maintain hydration and support metabolic functions. Additionally, broad-spectrum antibiotics were prescribed to prevent and treat potential infections, given the patient's compromised immune status.

Diagnostic investigations, including laboratory tests and imaging studies, were promptly conducted to assess the extent of the disease and guide further management decisions. These investigations included frequent complete blood counts and peripheral blood smears, serum bilirubin levels monitoring, and abdominal ultrasound examinations to monitor hepatosplenomegaly and assess organ function.

The therapeutic regimen adopted a conservative approach, focusing on supportive care and symptomatic management. This included frequent platelet transfusions (administered eight times) to manage thrombocytopenia and prevent bleeding complications. Packed red blood cell transfusions were administered twice to address anemia and support oxygen-carrying capacity. Supplementation with multivitamins and iron was initiated to support nutritional status and hematopoiesis. Ursofalk, a medication providing liver support, was administered to mitigate hepatomegaly and liver dysfunction. Moreover, the patient received a high-caloric formula feeding regimen to ensure adequate caloric intake and support optimal growth and development. Regular follow-up assessments were conducted to monitor the patient's clinical progress, including weight gain and vital signs stability, alongside laboratory parameters such as complete blood counts and serum bilirubin levels.

4. Comprehensive Assessment of Treatment Response

Before Treatment

The abdominal ultrasound findings revealed mild hepatosplenomegaly, with the liver measuring 8 cm in size and displaying a homogeneous echo pattern. No focal lesions or dilated intrahepatic biliary radicles were observed. The gallbladder appeared normal in size and wall thickness, without evidence of stones or sludge. The spleen exhibited mild splenomegaly, measuring 6.7 cm, while the pancreas and adrenals appeared unremarkable. Both kidneys showed normal size, position, and echogenicity, without any focal lesions or dilatations. The gastrointestinal tract, lymph nodes, and vasculature were within normal limits, with no significant abnormalities detected.

After Treatment

Following treatment, the abdominal ultrasound showed normalization of the liver size and echo pattern, with no evidence of bile duct dilation. The gallbladder remained unremarkable, and the spleen was within normal limits without splenomegaly. Similarly, the pancreas and adrenals appeared unremarkable. Both kidneys maintained their normal size, echogenicity, and parenchymal pattern.

No abnormalities were noted in the gastrointestinal tract, lymph nodes, or vasculature. These findings indicate a positive response to the therapeutic intervention.

Peripheral Smear

Before Treatment

The peripheral smear revealed normal total white blood cells (WBCs) with a left shift, 12% blasts, and absolute lymphocytosis. Mild macrocytic anemia and severe thrombocytopenia were noted.

After Treatment

Following treatment, the peripheral smear showed mild leucopenia with relative monocytosis, lymphocytosis, and absolute neutropenia. Additionally, mild normochromic, normocytic anemia with tear drop and target cells, along with moderate thrombocytopenia, was observed. Further follow-up with complete blood count and correlation with the patient's clinical condition are recommended.

Bilirubin Levels

Before Treatment

The total bilirubin level was elevated at 5.9 mg/dl, with the direct bilirubin level at 2.1 mg/dl.

After Treatment

Following treatment, the total bilirubin level decreased to 2.0 mg/dl, with the direct bilirubin level reduced to 0.8 mg/dl, both within the normal range.

These comprehensive findings indicate a favorable response to the therapeutic regimen, with improvement observed in multiple parameters, including hepatosplenomegaly, hematological indices, and bilirubin levels.

5. Discussion

The manuscript presents a detailed analysis of a rare case involving congenital leukemia in a 1-day-old male newborn

conceived through in vitro fertilization (IVF). It highlights the clinical significance and diagnostic challenges associated with neonatal congenital leukemia, emphasizing the complex interplay between genetic factors and IVF techniques. The clinical presentation of congenital leukemia in the neonatal period is discussed, encompassing varied manifestations such as hepatosplenomegaly, thrombocytopenia, and the presence of immature leukocytes in peripheral blood.

Recent advancements in molecular genetics have shed light on the genetic basis of congenital leukemia, particularly the role of the MLL gene and chromosomal translocations.[7] The manuscript underscores the importance of personalized diagnostic and therapeutic strategies in managing congenital leukemia, especially in the context of genetic abnormalities associated with IVF.

The observed genetic discordance between identical twins in the presented case underscores the complexity of genetic interactions and the multifactorial nature of phenotypic outcomes. Somatic mutations, chromosomal mosaicism, and epigenetic modifications are proposed mechanisms contributing to the phenotypic differences observed between the twins. Somatic mutations, particularly in genes like KMT2A, may lead to differential gene expression patterns, influencing phenotypic outcomes despite identical genetic makeup at conception. [8] Chromosomal mosaicism, particularly involving trisomy 21, may further contribute to discordant phenotypes by affecting gene expression and chromatin structure differently in each twin. [9] Moreover, epigenetic modifications, influenced by factors such as the IVF process and intrauterine environment, may contribute to differential gene expression and phenotypic variability between identical twins.[10] Understanding these molecular mechanisms is crucial for interpreting and managing genetic disorders effectively, especially in cases of discordant phenotypes among identical twins.

The manuscript raises important considerations regarding the impact of IVF on genetic stability and susceptibility to genetic disorders. While IVF has revolutionized reproductive medicine and helped many couples overcome infertility, it also poses potential risks, including alterations in gene expression, DNA methylation patterns, and chromosomal stability. [11] The observed discordance in Down syndrome manifestation and congenital leukemia between identical twins highlights the need for comprehensive strategies to mitigate genetic disorders in IVF-conceived pregnancies. Preimplantation genetic testing (PGT), optimization of culture conditions, parental genetic screening, research and development, and continued education and training are recommended approaches to reduce the incidence of genetic disorders in IVF-conceived pregnancies. [12] By integrating these strategies, clinicians and researchers can optimize reproductive outcomes and enhance the health and well-being of offspring conceived through IVF.

6. Conclusion

In conclusion, the manuscript provides valuable insights into the diagnosis, management, and implications of congenital leukemia, as well as the genetic discordance observed in identical twins conceived through IVF.

Understanding the molecular mechanisms underlying genetic disorders and the impact of IVF on genetic stability is essential for improving reproductive outcomes and guiding clinical practice. Further research is warranted to elucidate these mechanisms fully and develop effective strategies for preventing and managing genetic disorders in IVF-conceived

pregnancies.

Statements and Declarations

Informed consent

Before taking this case, information was given to the patient, and informed consent was obtained from the patient for follow-up and consent to share the investigations, figures, and any required data.

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Competing interests

The authors declare that there are no conflicts of interest.

Ethical approval statement or statement of informed consent for case studies

This case was conducted in accordance with the Declaration of Helsinki and meets the CARE guidelines. Informed consent was obtained from the patient for follow-up, including permission for publication of all photographs, lab, and images herein.

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