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Acute Myeloid Leukemia Arising in DNA Ligase IV Deficiency Syndrome: A Rare Case Report and Literature Review

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Abstract

Background

DNA ligase IV deficiency (LIG4 syndrome) is an exceptionally rare autosomal recessive disorder caused by mutations affecting the non-homologous end-joining DNA repair pathway. The syndrome is characterized by microcephaly, growth retardation, radiosensitivity, immunodeficiency, bone marrow failure, and predisposition to malignancy. Fewer than 30 cases have been reported worldwide, with hematologic malignancies representing uncommon but serious complications.

Case Presentation

We report a 21-year-old Saudi male referred for evaluation of pancytopenia and suspected inherited bone marrow failure syndrome. The patient had congenital dysmorphic features including short stature, microcephaly, and urogenital abnormalities (horseshoe kidney). Family history was notable for a similarly affected deceased sibling. Bone marrow examination demonstrated hypo cellularity with dysplastic changes and approximately 25% blasts, consistent with acute myeloid leukemia (AML) with myelodysplasia-related changes evolving from underlying myelodysplastic syndrome. Cytogenetic and fluorescence in situ hybridization (FISH) analyses revealed multiple abnormalities including trisomy 8, monosomy 11q, and 5q deletion. Genetic testing identified a homozygous LIG4 mutation, confirming DNA ligase IV deficiency syndrome.

Discussion

LIG4 deficiency is associated with defective DNA double-strand break repair, resulting in genomic instability, immunodeficiency, radiosensitivity, and increased susceptibility to hematologic malignancies. Progressive bone marrow failure and leukemic transformation are believed to result from accumulation of unrepaired DNA damage in hematopoietic stem cells. This case highlights the diagnostic challenges of inherited DNA repair disorders presenting in adulthood and emphasizes the importance of recognizing characteristic phenotypic features in patients with unexplained cytopenias and leukemia.

Conclusion

This report expands the clinical spectrum of LIG4 syndrome and underscores the need for heightened clinical suspicion of inherited DNA repair disorders in young patients presenting with bone marrow failure and AML. Early recognition is critical because of implications for treatment selection, radiation sensitivity, genetic counseling, and consideration of hematopoietic stem cell transplantation.

Keywords: DNA ligase IV deficiency, Acute myeloid leukemia, Inherited bone marrow failure syndrome, DNA repair disorder

Introduction

DNA ligase IV deficiency (LIG4 syndrome) is a rare autosomal recessive disorder caused by pathogenic mutations in the LIG4 gene, which encodes DNA ligase IV, a critical enzyme in the non-homologous end-joining (NHEJ) pathway responsible for DNA double-strand break (DSB) repair. The NHEJ pathway is essential for maintaining genomic integrity and plays a central role in the repair of DNA damage induced by physiologic cellular processes and environmental insults. In addition, this pathway is indispensable for V(D)J recombination during T- and B-lymphocyte maturation, making DNA ligase IV crucial for normal immune system development (Figure 1) [1].

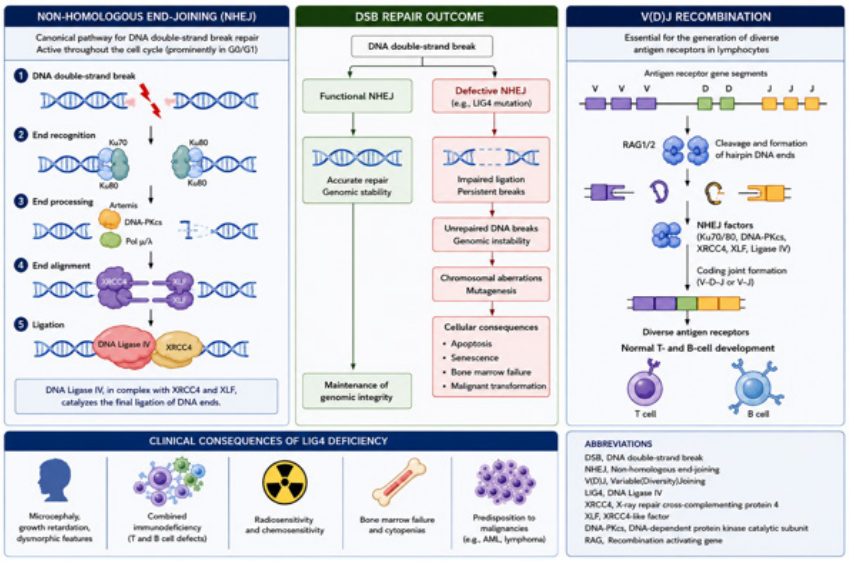

Figure 1. Role of DNA Ligase IV in Non-Homologous End-Joining (NHEJ) and V(D)J Recombination

DNA is continuously subjected to damage from endogenous and exogenous sources [1]. DNA double-strand breaks represent one of the most severe forms of DNA injury because unrepaired lesions may result in chromosomal instability, mutagenesis, apoptosis, or malignant transformation [2, 3]. Mammalian cells repair DSBs through two major pathways: homologous recombination, which is restricted to the late S and G2 phases, and non-homologous end joining, which operates throughout the cell cycle and predominates in G0 and G1 [1, 4]. The classical NHEJ pathway involves recognition of DNA breaks, processing of damaged DNA ends, and ligation of DNA strands through the coordinated activity of multiple repair proteins, including DNA ligase IV [1]. Individuals harboring mutations affecting DNA DSB repair pathways exhibit genomic instability and are predisposed to developmental abnormalities, immunodeficiency, bone marrow failure, and malignancy [1, 3].

In addition to preserving genomic stability, DNA DSB repair is essential for adaptive immunity, as V(D)J recombination depends on programmed DSB formation and repair to generate the diverse T-cell receptor and immunoglobulin repertoires [3, 4]. Consequently, impairment of NHEJ-mediated repair disrupts normal lymphocyte maturation and may result in combined immunodeficiency with varying degrees of T- and B-cell dysfunction [5].

Clinically, LIG4 syndrome demonstrates marked phenotypic heterogeneity. Common manifestations include congenital microcephaly, severe growth restriction, developmental delay, dysmorphic facial features, radiosensitivity, and combined immunodeficiency [6]. Additional reported findings include skeletal abnormalities, skin disorders, hypogonadism, bone marrow hypoplasia, and progressive pancytopenia (Table 1). The severity of immunodeficiency ranges from mild lymphopenia to severe combined immunodeficiency (SCID), and affected patients are at increased risk of recurrent infections and hematologic malignancies [7].

Table 1: Clinical Manifestations Reported in DNA Ligase IV Deficiency Syndrome

Physical features	Microcephaly
	Growth restriction
	"Bird-like" or "Seckel syndrome-like" facies
	Bilateral epicanthic folds
	Hypogonadism
	Urogenital abnormalities
	External ear abnormalities
Bone abnormalities	Bone Hypoplasia
	Syndactyly
	Polydactyly
	Congenital Hip Dysplasia
Skin conditions	Photosensitivity
	Psoriasis
	Eczema
	Widespread Ecchymosis
	Hypopigmentation
	Extensive Plantar Warts

The LIG4 gene is located on chromosome 13q33-q34, a region implicated in several hematologic malignancies, including Burkitt lymphoma and acute lymphoblastic leukemia [6]. Experimental murine models of LIG4 deficiency have reproduced the human phenotype, including immunodeficiency, radiosensitivity, and progressive bone marrow failure [8]. Accumulation of unrepaired DNA damage within hematopoietic stem cells is believed to contribute to stem cell exhaustion, marrow failure, and leukemogenesis [9].

Despite increasing recognition of inherited DNA repair disorders, LIG4 deficiency remains exceptionally rare, with fewer than 30 cases reported worldwide to date [1]. Hematologic malignancies associated with LIG4 deficiency are uncommon but represent a major cause of morbidity and mortality. Herein, we describe a rare case of a young Saudi male with congenital dysmorphic features and bone marrow failure who subsequently developed acute myeloid leukemia with myelodysplastic-related changes in the setting of confirmed DNA ligase IV deficiency.

Clinical Presentation and Complications

A 21-year-old Saudi male was initially admitted to King Fahad Hospital with pancytopenia manifested by neutropenia, anemia, and thrombocytopenia, requiring multiple packed red blood cell and platelet transfusions. Four months later, he was referred to King Faisal Specialist Hospital and Research Centre for further evaluation with a preliminary impression of Fanconi anemia.

The patient had congenital dysmorphic features since birth, including short stature and microcephaly. Physical examination was otherwise unremarkable. Abdominal ultrasonography revealed a horseshoe kidney consistent with urogenital malformation. He had no history of smoking, alcohol use, previous surgeries, major illnesses, or chronic medication use. Socially, the patient was unemployed and had discontinued college education.

Family history was notable for possible hereditary disease involvement. The patient had six brothers and ten sisters from different mothers. His parents were non-consanguineous and had no known medical comorbidities. One sister reportedly had similar dysmorphic features and died undiagnosed in 2013, while another sister was suspected to have the same disorder.

Bone marrow examination was performed twice for morphologic assessment. The initial bone marrow biopsy performed at King Fahad Hospital demonstrated overall hypocellularity with trilineage hypoplasia and no evidence of fibrosis or leukemic infiltration. A repeat bone marrow biopsy performed at King Faisal Specialist Hospital showed a hypocellular marrow with an overall cellularity of approximately 30–40%. Scattered small hypolobated megakaryocytes were identified, and clusters of immature cells constituted approximately 25% of marrow cellularity. Granulopoiesis demonstrated marked maturation arrest, while erythropoiesis appeared relatively preserved.

Peripheral blood counts revealed severe pancytopenia with a white blood cell count of 1.37 × 10^9/L, hemoglobin of 94 g/L, platelet count of 56 × 10^9/L, and red blood cell count of 3.30 × 10^12/L. Red blood cell indices showed normocytic normochromic anemia with a mean corpuscular volume of 86.7 fL and mean corpuscular hemoglobin concentration of 329 g/L. Differential count demonstrated neutropenia with relative lymphocytosis and circulating immature myeloid forms. Flow cytometric analysis could not be performed because of insufficient cellularity.

Genetic evaluation identified a homozygous LIG4 mutation (LIG4 HMZ), confirming DNA ligase IV deficiency syndrome. Chromosomal breakage studies were negative. A next-generation sequencing (NGS) myeloid panel was ordered to further characterize the molecular profile of the leukemia; however, the test failed and no result was obtained. However, fluorescence in situ hybridization (FISH) analysis demonstrated multiple cytogenetic abnormalities, including trisomy 8/+8q involving RUNX1T1 (ETO) in 16% of nuclei, monosomy 11q involving the MLL locus in 95% of nuclei, deletion of EGR1 (5q31) in 94% of nuclei, and trisomy 8 (D8Z2) in 11% of nuclei.

Based on morphologic findings, cytopenias, dysplastic marrow changes, and increased blast percentage, the patient was diagnosed with acute myeloid leukemia with myelodysplasia-related. Changes arising from an underlying myelodysplastic syndrome in the setting of confirmed DNA ligase IV deficiency. The patient's hematologic, bone marrow, cytogenetic, and molecular findings are summarized in (Table 2)

Table 2. Laboratory, Bone Marrow, Cytogenetic, and Molecular Findings in the Present Case

Category	Finding	Result / Description
Complete Blood Count	White blood cell count	1.37 × 10^9/L
	Hemoglobin	94 g/L
	Red blood cell count	3.30 × 10^12/L
	Hematocrit	0.286
	Platelet count	56 × 10^9/L
	Mean corpuscular volume (MCV)	86.7 fL
	Mean corpuscular hemoglobin (MCH)	28.5 pg
	Mean corpuscular hemoglobin concentration (MCHC)	329 g/L
	Red cell distribution width (RDW)	13.5%
Peripheral Blood Differential	Neutrophils (Polys)	18%

	Bands	4%
	Lymphocytes	64%
	Monocytes	1%
	Eosinophils	2%
	Atypical lymphocytes	4%
	Metamyelocytes	6%
	Myelocytes	2%
	Reticulocyte count	107 × 10^9/L
Bone Marrow Findings	Initial bone marrow biopsy	Hypocellular marrow with trilineage hypoplasia
	Fibrosis/infiltration	Not identified
	Repeat bone marrow biopsy cellularity	Approximately 30–40%
	Megakaryocytes	Small hypolobated dysplastic forms
	Blast percentage	Approximately 25% of marrow cellularity
	Granulopoiesis	Marked maturation arrest
	Erythropoiesis	Relatively preserved
	Flow cytometry	Not performed due to insufficient cellularity
Cytogenetic Findings	Chromosomal breakage study	Negative
	RUNX1T1 (ETO) abnormality	Trisomy +8/+8q in 16% of nuclei
	MLL abnormality	Monosomy 11q in 95% of nuclei
	EGR1 (5q31) deletion	Detected in 94% of nuclei
	Trisomy 8 (D8Z2)	Detected in 11% of nuclei
Molecular Findings	LIG4 mutation	Homozygous LIG4 mutation (LIG4 HMZ)
	NGS myeloid panel	Ordered; test failed (no result obtained)
Final Diagnosis	Hematologic diagnosis	Acute myeloid leukemia with myelodysplasia-related changes arising from underlying myelodysplastic syndrome in the setting of DNA ligase IV deficiency

Discussion

DNA ligase IV (LIG4) deficiency is an exceptionally rare inherited DNA repair disorder characterized by defective non-homologous end-joining (NHEJ), resulting in impaired repair of DNA double-strand breaks, genomic instability, radiosensitivity, immunodeficiency, bone marrow failure, and predisposition to malignancy [1]. Since its initial description, fewer than 30 cases have been reported worldwide, and the phenotypic spectrum remains incompletely defined. The present case highlights several classic manifestations of LIG4 syndrome, including congenital dysmorphic features, microcephaly, growth restriction, marrow failure, and leukemic transformation.

Microcephaly represents the most commonly reported clinical manifestation of LIG4 deficiency and has been described in the

majority of published cases [1]. Growth restriction and developmental abnormalities frequently coexist and may begin during intrauterine development. Additional phenotypic abnormalities reported in the literature include characteristic facial dysmorphism, skeletal abnormalities such as syndactyly and hip dysplasia, skin manifestations, hypogonadism, and neurodevelopmental impairment [1, 10, 11]. Our patient demonstrated several characteristic features including congenital microcephaly, short stature, and urogenital abnormality in the form of a horseshoe kidney, supporting the syndromic nature of the disease.

The immunologic manifestations of LIG4 deficiency are highly variable and range from mild combined immunodeficiency to severe combined immunodeficiency (SCID) [1, 6, 10]. Previous reports have described profound T- and B-cell lymphocytopenia with varying degrees of hypogammaglobulinemia [12]. Four reported patients developed SCID, and one case was associated with features of Omenn syndrome [1, 13-15]. Interestingly, despite the severe genomic instability associated with this disorder, some patients may initially present predominantly with bone marrow failure or growth abnormalities rather than overt immunodeficiency, potentially delaying diagnosis [1, 16]. In the present case, the patient primarily presented with pancytopenia and marrow failure without a prior history of recurrent severe infections, illustrating the broad phenotypic variability of the syndrome.

Bone marrow failure is a major complication of LIG4 deficiency and is believed to result from progressive accumulation of unrepaired DNA damage within hematopoietic stem cells leading to apoptosis and stem cell exhaustion [17]. Several studies have demonstrated progressive cytopenias requiring transfusion support in affected individuals [16]. In the cohort reported by Murray et al., nine patients developed significant cytopenias related to marrow failure, and several required hematopoietic stem cell transplantation (HSCT) [16]. Our patient similarly developed severe pancytopenia with hypocellular marrow findings and trilineage dysplasia, ultimately progressing to acute myeloid leukemia (AML) with myelodysplasia-related changes.

Malignancy remains one of the most serious complications of LIG4 deficiency, reflecting the profound genomic instability associated with defective DNA repair. However, hematologic malignancies remain relatively uncommon because of the rarity of the disorder itself. Previous reports have described lymphoma in several patients, including Epstein–Barr virus-associated lymphoproliferative disease, while isolated cases of leukemia and squamous cell carcinoma have also been documented [18-22]. Our patient developed AML arising from an underlying myelodysplastic process, further supporting the association between defective DNA repair pathways and leukemogenesis. Cytogenetic analysis demonstrated multiple chromosomal abnormalities including monosomy 11q, trisomy 8, and deletion 5q, findings consistent with genomic instability and secondary leukemic transformation.

The diagnosis of LIG4 deficiency requires a high degree of clinical suspicion, particularly in patients presenting with microcephaly, growth restriction, cytopenias, immunodeficiency, or unusual sensitivity to radiation [1]. Bone marrow hypoplasia, lymphopenia, hypogammaglobulinemia, and chromosomal instability may provide additional diagnostic clues. Functional confirmation of radiosensitivity using clonogenic survival assays has historically been considered an important diagnostic tool, followed by molecular confirmation through genetic testing [23]. In our patient, the diagnosis was established through identification of a homozygous LIG4 mutation in the setting of characteristic clinical and hematologic findings.

Recognition of LIG4 deficiency has important therapeutic implications. Patients demonstrate marked hypersensitivity to ionizing radiation and DNA-damaging agents, which may complicate conventional chemotherapy and conditioning regimens used for malignancy treatment or HSCT [24]. Early diagnosis is therefore essential to guide treatment modifications, avoid excessive treatment-related toxicity, provide genetic counseling, and facilitate appropriate donor selection and transplant planning when indicated.

The cytogenetic profile observed in our patient provides additional insight into the mechanism of leukemic transformation in LIG4 deficiency. The combination of monosomy 11q, trisomy 8, and deletion 5q reflects the chromosomal instability expected

when non-homologous end-joining is impaired, as unrepaired double-strand breaks accumulate and drive complex karyotypic evolution. Deletion of 5q and abnormalities involving the MLL locus on 11q are recurrent findings in myelodysplastic syndrome and secondary acute myeloid leukemia, and their emergence in this setting is consistent with the hypothesis that progressive accumulation of unrepaired DNA damage within hematopoietic stem cells promotes clonal selection, stem cell exhaustion, and ultimately leukemogenesis [8, 9, 17]. The transformation from an initially hypocellular, dysplastic marrow to overt acute myeloid leukemia in our patient illustrates this stepwise progression and reinforces the link between defective DNA repair and myeloid malignancy. A next-generation sequencing (NGS) myeloid panel was ordered to further define the molecular landscape of the leukemia, but the assay failed and no result could be obtained; this represents a limitation of the present case, as additional somatic mutations relevant to prognosis and to the mechanism of leukemic transformation could not be assessed.

The therapeutic management of malignancy in LIG4 deficiency is particularly challenging and differs substantially from that of sporadic acute myeloid leukemia. Because affected cells cannot efficiently repair double-strand breaks, patients exhibit pronounced hypersensitivity to ionizing radiation and to DNA-damaging chemotherapeutic agents such as alkylators and topoisomerase inhibitors, which form the backbone of conventional induction and conditioning regimens [24]. Standard-intensity chemotherapy may therefore precipitate severe, prolonged, and potentially fatal toxicity, and total body irradiation is generally contraindicated. When hematopoietic stem cell transplantation is pursued for marrow failure or leukemia, reduced-intensity and radiation-free conditioning protocols are preferred to limit regimen-related toxicity while still achieving engraftment [16]. Reported transplant outcomes in LIG4 deficiency remain limited and variable, underscoring the need for individualized, attenuated treatment planning and close multidisciplinary involvement of hematology, transplantation, and clinical genetics services.

Beyond the index patient, recognition of LIG4 deficiency carries important implications for the wider family. The autosomal recessive inheritance of the disorder, together with the history of a similarly affected, undiagnosed deceased sibling and a second sibling with suspected disease, highlights the value of cascade genetic testing and formal genetic counseling. Confirmation of the homozygous LIG4 mutation in our patient permits carrier identification, informed reproductive counseling, and earlier surveillance of at-risk relatives, who may otherwise present late with cytopenias or malignancy. Heightened awareness of the syndrome may also prevent inadvertent diagnostic radiation exposure and the use of standard-dose chemotherapy in undiagnosed relatives. These considerations emphasize that the diagnosis of an inherited DNA repair disorder is not only of academic interest but directly influences treatment selection, family screening, and long-term surveillance strategies [1, 6].

This case expands the limited literature describing hematologic malignancy in patients with LIG4 deficiency and underscores the importance of considering inherited DNA repair disorders in young patients presenting with marrow failure, congenital anomalies, and leukemia. Early recognition of these syndromes is critical because of their unique biologic behavior, treatment challenges, and implications for long-term management.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Ethics Approval

The study was approved by the Institutional Ethics Committee of King Faisal Sepecilist and research Centre.

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