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– CASE REPORT –

Immune Dysfunction and Hematologic Malignancies in Young Adults: A Two-Case Series Highlighting Germline Predisposition, DNA Repair Defects, and Primary Antibody Deficiency

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Abstract

Aim: *This case series describes two young adults with aggressive hematologic malignancies and underlying immune dysfunction, in whom germline cancer predisposition syndromes were identified or strongly suspected. The study intends to highlight the diagnostic and interpretive challenges of tumor-oriented sequencing in this clinical context.*

Methods: *We conducted a retrospective analysis of clinical, immunological, and genetic data from two patients referred to a tertiary hematology center for aggressive or recurrent hematologic malignancies associated with severe infectious complications and immune dysregulation. Targeted next-generation sequencing (NGS) panels were used in all cases, and confirmatory germline testing using non-hematopoietic tissue was performed when a hereditary predisposition syndrome was suspected.*

Results: *Case 1 (M.E.G., 24 years) carried a heterozygous germline DDX41 variant and presented with peripheral T-cell lymphoma (Lennert variant), treatment-refractory disease, and a severe infectious burden. Case 2 (N.S.L., 24 years) had congenital IgG/IgA deficiency and was ultimately diagnosed with Nijmegen breakage syndrome due to a homozygous pathogenic NBN variant, and developed an aggressive Epstein–Barr virus (EBV)-associated B cell lymphoma against a background of primary immunodeficiency.*

Conclusions: *Systematic germline evaluation should be considered for young patients with aggressive or multiple hematologic malignancies and unexplained immune dysfunction. Early identification of inherited cancer predisposition syndromes has major consequences for treatment strategies, donor selection for transplantation, family testing, and long-term oncologic surveillance.*

Keywords: *immune dysfunction; hematologic malignancies; DDX41; NBN; primary antibody deficiency; Nijmegen breakage syndrome; germline predisposition*

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Introduction

In the era of next-generation sequencing (NGS), immune dysfunction increasingly serves as an early manifestation of underlying inborn errors of immunity and inherited cancer predisposition syndromes. Large registry-based and cohort studies have documented an excess of hematologic malignancies, particularly non-Hodgkin lymphomas, among patients with primary antibody deficiencies and combined immune defects (1). In recent years, accumulating evidence has further highlighted the complex relationship between immune dysregulation and hematologic malignancies in young adults, particularly in the context of germline predisposition syndromes and DNA repair defects, emphasizing the importance of integrated clinical, immunological, and genetic evaluation(2).

Common variable immunodeficiency (CVID) and related antibody-deficiency disorders are among the best characterized in this regard, with distinct clinical phenotypes associated with autoimmunity, granulomatous disease, and malignancy (1,3,4). In CVID and adult primary immunodeficiency cohorts, lymphomas—predominantly diffuse large B-cell lymphoma (DLBCL)—are a major cause of morbidity and mortality (3).

Contemporary frameworks emphasize integrating clinical "red flags" with structured laboratory evaluation and targeted genetic testing (4). Major warning signs include severe, recurrent, or opportunistic infections; early disease onset; failure to thrive; dysmorphic features; microcephaly or short stature; persistent cytopenias or macro- or microcytosis; and hematologic malignancies at a young age. A minimal diagnostic workup should include a complete blood count with peripheral smear; quantitative immunoglobulins (IgG, IgA, IgM, and, when available, IgG subclasses); lymphocyte subpopulations by flow cytometry; inflammatory and organ function markers; and a structured three-generation family history (1).

Genetic testing approaches have evolved from single-gene analysis to NGS-based immune deficiency and cancer predisposition panels, and, in complex phenotypes, to whole-exome or whole-genome sequencing. Periodic reinterpretation and family segregation studies are often required to improve variant classification as new disease genes and phenotypes are described (5).

DNA (Deoxyribonucleic Acid) repair disorders are a critical differential diagnosis in patients with combined immunodeficiency and early-onset malignancy. Nijmegen breakage syndrome (NBS), caused by biallelic pathogenic variants in NBN, is characterized by progressive microcephaly, growth retardation, recurrent sinopulmonary infections, combined T- and B-cell deficiency, and a markedly increased risk of lymphoma. Mechanistically, dysfunction of the MRN (MRE11–RAD50–NBN) complex impairs the detection and repair of DNA double-strand breaks, leading to genomic instability. Recognition of this triad is essential, as confirmation of a DNA repair disorder directly modifies management, including avoidance of ionizing radiation, adapted oncologic protocols, lifelong malignancy surveillance, and tailored immunization strategies (1).

In parallel, germline variants in classical hematologic predisposition genes, such as DDX41, are increasingly identified through tumor-oriented NGS panels used in myeloid and lymphoid neoplasms. Germline DDX41 variants are now recognized as a frequent cause associated with familial myeloid neoplasms, and multiple reviews have summarized the spectrum of malignancies arising in the context of primary and secondary immune deficiencies (6).

In this context, we report two illustrative cases at the intersection of immune dysfunction, hematologic malignancy, and germline predisposition: a young adult with a germline DDX41 variant and peripheral T-cell lymphoma and a young adult with Nijmegen breakage syndrome and EBV-associated lymphoma. These cases emphasize the interpretive challenges of tumor-based sequencing when hereditary predisposition remains not initially suspected and underline the clinical impact of identifying constitutional variants in patients with immune dysregulation (7).

Materials and Methods

This retrospective case series was conducted at the Department of Hematology at the Fundeni Clinical Institute in Bucharest, Romania, a national tertiary referral center. Two patients (Cases 1–2) with hematologic malignancies and documented or suspected immune dysfunction were included.

Clinical data were extracted from electronic medical records, discharge summaries, laboratory databases, and genetic testing reports. The retrospective analysis comprised demographic characteristics, temporal parameters (age at onset of infectious manifestations and age at hematologic malignancy diagnosis), disease-specific features (type and stage of hematologic malignancy), therapeutic history and response, documented infectious episodes with associated complications, comprehensive immunological

investigations (quantitative serum immunoglobulins, complement fractions, inflammatory markers, and lymphocyte immunophenotyping by flow cytometry when available), and molecular genetic testing results.

Interpretation of immunological abnormalities and their association with malignancy was informed by published data on CVID, adult primary immunodeficiencies, and lymphoma risk (8). Genetic testing consisted of targeted NGS panels for hematologic malignancies. When clinical features suggested a hereditary predisposition syndrome (young age at onset, multiple malignancies, characteristic immune phenotype), germline testing was performed using non-hematopoietic tissue (buccal swab), and variants were classified according to ACMG/AMP guidelines (5). Somatic variants identified by tumor-only sequencing were initially classified using standard somatic variant tiering systems (6).

All data were anonymized before analysis. The study was conducted in accordance with institutional ethical requirements.

Results

Case 1 — M.E.G., 24 years: germline DDX41 variant and peripheral T-cell lymphoma

A 24-year-old female was diagnosed with peripheral T-cell lymphoma, lymphoepithelioid (Lennert) variant, Ann Arbor stage IVB. The disease had a highly aggressive, treatment-refractory course, requiring CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) /CHOEP (Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisone) -based chemotherapy, multiple salvage regimens, brentuximab vedotin, and ultimately high-dose chemotherapy with BEAM (Carmustine, Etoposide, Cytarabine, Melphalan conditioning regimen) conditioning followed by autologous hematopoietic stem cell transplantation.

Flow cytometric immunophenotyping revealed marked absolute lymphopenia characterized by severe B-cell depletion and partial NK-cell deficiency. T-cell populations demonstrated proportionally intact distribution but diminished absolute counts across CD3+, CD4+, and CD8+ subsets; the CD4/CD8 ratio remained within physiological limits. Collectively, these data established pan-lymphocytopenia encompassing T-, B-, and NK-cell compartments. This immunological constellation is consistent with combined cellular and humoral immune dysfunction exhibiting a CVID-like phenotype, thereby conferring increased vulnerability to opportunistic infections and immune dysregulation within the framework of underlying constitutional genetic predisposition.

The clinical course was initially complicated by recurrent severe infections, including Gram-negative sepsis, recurrent urinary tract infections, and cytomegalovirus (CMV) reactivation. The patient experienced prolonged neutropenia with delayed hematologic recovery after chemotherapy cycles, necessitating multiple hospitalizations for febrile neutropenia. Additional complications included posterior reversible encephalopathy syndrome (PRESS), transient pericardial effusion, and progressive hepatosplenomegaly with persistent lymphadenopathy on imaging.

Initial virological evaluation demonstrated detectable Parvovirus B19 DNA (667 IU/ml) in the absence of CMV and Epstein–Barr virus (EBV) replication, while immunological assessment revealed profound hypogammaglobulinemia with nadir immunoglobulin levels of IgG 2.4 g/L, IgA <0.224 g/L, and IgM <0.191 g/L, consistent with severe humoral immune dysfunction. Subsequent longitudinal monitoring of Parvovirus B19 persistence clearance, with later episodes of CMV and EBV reactivation during periods of immunosuppressive therapy, a dynamic virological profile indicative of impaired viral immune control in the context of underlying immune deficiency and treatment-related immunosuppression, which likely contributed to the patient's infectious complications, cytopenias, and delayed hematologic recovery.

Given the young age at diagnosis, severe infectious burden, and prolonged cytopenias, germline predisposition was suspected. Targeted NGS and confirmatory germline testing identified a heterozygous DDX41 variant, c.811C>T (p.Arg271Trp), classified as likely pathogenic per ACMG/AMP criteria (5). Additional variants of uncertain significance were detected in CACUL1 and NECTIN2, with unclear clinical impact.

DDX41 encodes a DEAD-box RNA helicase involved in nucleic acid sensing, innate immune signaling, and maintenance of genomic stability. Inherited and somatic defects in DDX41 have been associated predominantly with familial myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), with most cases presenting in late adulthood. However, accumulating evidence indicates a broader spectrum that may include immune dysregulation, chronic cytopenias, and occasional lymphoid neoplasms (6).

Identifying a germline DDX41 variant in this patient has several implications: (i) lifelong hematologic surveillance

for myeloid neoplasms; (ii) structured genetic counseling and cascade testing of first-degree relatives; and (iii) mandatory DDX41 testing of any potential related stem cell donors, given published reports of donor-derived leukemia and adverse transplant outcomes in unrecognized germline carriers (5,6).

Peripheral T-cell lymphomas are associated with a poor prognosis, with a reported 5-year overall survival of approximately 20–30% in advanced-stage disease. The aggressive clinical course observed in our patient, characterized by treatment refractoriness, severe infectious complications, and the need for high-dose chemotherapy followed by autologous transplantation, is consistent with this unfavorable natural history. Although germline DDX41–associated hematologic malignancies—predominantly myeloid neoplasms—have been reported to have relatively favorable outcomes compared with sporadic cases, there is currently no evidence that DDX41 confers a prognostic advantage in lymphoid malignancies. The clinical trajectory in this patient, therefore, appears primarily driven by the intrinsic biology of peripheral T-cell lymphoma and the coexistence of immune dysfunction rather than by the germline variant itself.

Case 2 — N.S.L., 24 years: Nijmegen breakage syndrome and EBV-associated lymphoma

A 24-year-old male presented with an aggressive B-cell lymphoproliferative disorder. He had a history of congenital antibody deficiency, with combined IgG and IgA deficiency documented since age 7 and recurrent, severe upper and lower respiratory infections requiring repeated hospitalizations. The patient received intermittent long-term immunoglobulin replacement therapy and did not maintain regular immunologic follow-up.

In young adulthood, the diagnosis of plasmablastic or diffuse large B-cell lymphoma was made by histopathology and immunophenotyping of the extensive lymphadenopathy and visceral involvement. EBV positivity was documented, implicating chronic viral stimulation in lymphomagenesis. The oncologic course was further complicated by prolonged neutropenia and several infectious episodes, including SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection and bacterial sepsis.

Multiparameter flow cytometric immunophenotyping of peripheral blood disclosed a clonally expanded mature B-cell population accounting for approximately 40% of circulating lymphocytes, demonstrating lambda light-chain monoclonality with the following antigenic profile: CD19+, CD45+, CD20 (dim expression), CD5−, CD23−, CD200−, CD79b+, CD38−, CD10−, surface IgM+, CD81+, CD11c+, CD22 (dim expression), CD49d (dim expression), and HLA-DR+. This immunophenotypic constellation corresponded to the clonal B-cell population subsequently confirmed in the DLBCL tissue specimen by histomorphology and immunohistochemistry. Within the clinical context of severe hypogammaglobulinemia and biallelic NBN-associated DNA repair deficiency characteristic of Nijmegen breakage syndrome, these findings corroborate a clonal lymphoproliferative disorder emerging from the convergence of impaired adaptive immune surveillance and constitutional chromosomal instability.

Immunologic workup at the time of lymphoma diagnosis revealed profound hypogammaglobulinemia with extremely low IgG and IgA levels (IgG 2.18 g/L, IgA 0.15 g/L) and relatively elevated IgM (2.27 g/L), accompanied by a markedly reduced gamma-globulin fraction on serum protein electrophoresis. C-reactive protein, ferritin, and fibrinogen were elevated, and significant hepatic enzyme abnormalities and hyponatremia were observed during infectious and inflammatory episodes. Complement fractions (C3, C4) were within normal limits. This profile is compatible with a primary antibody deficiency with impaired class-switch recombination, a pattern associated with increased risk of lymphoproliferative disease in CVID-like disorders (8).

Given the constellation of early-onset immune deficiency, recurrent infections, EBV-associated aggressive lymphoma, and suspected genomic instability, a DNA repair disorder was strongly suspected. Subsequent genetic testing identified a homozygous pathogenic variant in NBN, confirming the diagnosis of Nijmegen breakage syndrome. This is consistent with the description of NBS as a combined immunodeficiency with marked lymphoma risk, radiosensitivity, and increased chemotherapy toxicity (1,8,9).

Published series indicate that patients with primary antibody deficiencies and combined immunodeficiencies are at significantly increased risk of B-cell lymphomas, often in association with EBV infection (8). The current case fits this pattern and also illustrates the additional risk conferred by a defined DNA repair defect.

Management included repeated intravenous immunoglobulin (IVIG) infusions, prolonged courses of antimicrobial therapy, and rigorous infectious surveillance, including EBV and CMV viral load

monitoring. From a hereditary perspective, the presence of a homozygous NBN variant has major implications for family members: heterozygous carriers, although not affected by the full NBS phenotype, have been shown to have an increased lifetime risk of solid tumors, particularly ovarian cancer (1,8–10). In addition, potential related stem cell donors must undergo targeted NBN testing to avoid the use of carriers in allogeneic transplantation (1,8–10).

The patient had a rapidly progressive clinical course, with an overall survival of approximately eight months from lymphoma diagnosis (August 2021 to April 2022), reflecting the aggressive disease course typically observed in lymphoid malignancies arising in the context of Nijmegen breakage syndrome (NBS). Published data indicate that patients with NBS have a markedly increased risk of early-onset lymphoid malignancies and poor outcomes, largely driven by underlying genomic instability, combined immunodeficiency, and increased treatment-related toxicity. The short survival observed in our case is therefore consistent with the unfavorable prognosis reported in DNA repair disorders complicated by lymphoma (1).

Feature	Case 1: M.E.G., 24 years	Case 2: N.S.L., 24 years
Malignancy	Peripheral T-cell lymphoma (Lennert variant)	EBV-associated aggressive B-cell lymphoma
Immune background	Immune dysregulation DDX41 IgA <0.224 g/L IgM <0.191 g/L IgG 2.4 g/L, , and	Congenital IgG/IgA deficiency; Nijmegen breakage syndrome IgA 0.15 g/L IgM: 2.27 g/L IgG: 2.18 g/L
Genetics	Germline DDX41 variant (likely pathogenic)	Homozygous pathogenic NBN variant
Age at first malignancy	24 years	24 years
Viral infections	Parvovirus B19, CMV, EBV	CMV, EBV, SARS-CoV-2
Transplant status	Autologous HSCT	No HSCT reported

Figure1. *Comparative overview of the two cases*

Discussion

These two case series illustrate the heterogeneity and complexity of germline predisposition to hematologic malignancies in the context of immune dysfunction and are consistent with existing evidence on malignancy risk in primary immunodeficiencies (1).

Case 1 describes a germline DDX41 variant in a young adult with peripheral T-cell lymphoma. Although DDX41 germline mutations have primarily been associated with adult-onset myeloid neoplasms, this case supports an expanded clinical spectrum that includes lymphoid malignancy and immune dysregulation. This observation aligns with emerging data indicating that predisposition genes classically linked to a single lineage can underlie a broader range of hematologic phenotypes (6).

Case 2 is a prototypical DNA repair disorder, with confirmed Nijmegen breakage syndrome explaining the combination of congenital antibody deficiency and EBV-driven aggressive lymphoma. This is consistent with previous reports showing that NBS and related DNA repair defects confer a high risk of lymphoma, increased treatment toxicity, and distinctive immunologic profiles (1). The hypogammaglobulinemia and recurrent infections observed in this patient are findings from large CVID and primary immunodeficiency cohorts in which lymphoma is a leading complication (8).

The association between inborn errors of immunity and malignancy is well documented (1). Underlying mechanisms include impaired antigen presentation, defects in T-cell activation, altered B-cell maturation, and chronic immune activation, all of which favor clonal selection and malignant transformation. Persistent viral infections, particularly EBV, are additional risk factors for lymphomagenesis in immunocompromised hosts (9). DNA repair defects, including those involving NBN, further increase genomic instability (1).

The widespread use of NGS panels in hematology has led to frequent identification of variants in DDX41 and other predisposition genes (5,6). When molecular analyses are

performed exclusively on tumor tissue, germline variants may be misclassified as somatic. Confirming the variant's presence in non-hematopoietic tissue is essential when the clinical presentation suggests hereditary predisposition.

Accumulating evidence on germline predisposition syndromes, including those associated with DDX41 and its variants, as well as DNA repair disorders such as NBS, underscores the crucial importance of incorporating genetic information into donor selection strategies for allogeneic hematopoietic stem cell transplantation. Use of related donors harboring the pathogenic familial variant has been linked to donor-derived leukemia and adverse clinical outcomes (6). Moreover, in DNA repair disorders, both homozygous patients and heterozygous carriers may show greater sensitivity to conditioning therapy and increased susceptibility to secondary neoplasms (1).

Limitations

This study is limited by its retrospective design and by descriptions of two cases from a single center. Segregation analysis and family testing for the DDX41 variant were not performed, precluding definitive pathogenic classification according to current ACMG/AMP criteria (5). Follow-up duration and treatment exposures also varied substantially between cases, limiting the ability to draw comparative conclusions about outcomes. Nonetheless, the cases provide clinically meaningful insight into the diagnostic and management challenges at the interface of immune dysfunction, germline predisposition, and hematologic malignancy in young adults, and are consistent with patterns reported in larger primary immunodeficiency and malignancy cohorts (3,8,10–12).

Conclusions

Young adults and middle-aged patients presenting with aggressive or multiple hematologic malignancies and unexplained immune dysfunction should undergo systematic evaluation for underlying inborn errors of immunity and germline cancer predisposition, consistent with existing evidence from CVID and adult primary immunodeficiency cohorts (1). Although essential for therapeutic decision-making, tumor-oriented NGS is insufficient to identify hereditary syndromes. When clinical features raise suspicion of germline predisposition—such as early age at onset, multiple primary hematologic malignancies, or characteristic immune phenotypes—confirmatory germline testing using non-hematopoietic tissue is required (5).

In hereditary disorders associated with immune deficiency and cancer predisposition, systematic family testing is mandatory whenever hematopoietic stem cell transplantation from related donors is considered to avoid using an affected or carrier donor. This principle is particularly critical in DNA repair disorders, including Nijmegen breakage syndrome (1). Heterozygous carriers of DNA repair disorder variants (such as NBN heterozygotes), although not clinically affected by the full syndrome, have an increased lifetime risk of solid tumors in adulthood, with ovarian cancer being among the most consistently reported associations. Cascade family testing, structured genetic counseling, and tailored long-term oncologic surveillance should therefore be standard components of care (1).

Germline variants in genes such as DDX41 may present with broader phenotypes than classically described, including lymphoid and mature T-cell neoplasms in individuals with immune dysfunction (6). Primary antibody deficiencies require consistent immunoglobulin replacement therapy and structured infectious prophylaxis to reduce the risk of lymphoproliferative disease (8).

A multidisciplinary approach that integrates hematology, clinical immunology, medical genetics, and infectious diseases is crucial for translating genetic and immunological discoveries into personalized treatment strategies, suitable donor selection, and long-term monitoring plans for patients and their at-risk relatives. The prognosis for individuals with germline predisposition syndromes and immune dysfunction remains challenging and heavily dependent on early diagnosis, access to effective therapies, and consistent follow-up. In hematologic malignancies linked to DDX41 mutations, initial treatment responses in myeloid neoplasms are often favorable; however, the risk of additional cancers and treatment-related complications increases over time, particularly when immune issues or lymphoid diseases are present (4).

Patients with DNA repair disorders, such as Nijmegen breakage syndrome, face an even graver outlook because of heightened radiosensitivity, chemotherapy toxicity, and a significantly increased lifetime risk of multiple cancers. Immunoglobulin replacement therapy and rigorous infection control can enhance quality of life and reduce lymphoma risk in antibody-deficient individuals, but the development of aggressive lymphoma associated with DNA repair defects often results in poor survival despite intensive treatments. There is a pressing need for long-term, prospective studies to refine treatment approaches,

improve individual risk prediction, and establish evidence-based surveillance protocols for these complex, high-risk groups.

Ethics Statement and Conflict of Interest Disclosures

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Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by the patient participant in this study.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/ or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests: The authors declared that they have no competing interests.

The use of generative AI and AI-assisted technologies: AI technologies were used solely to refine English language and spelling.

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