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Review

Lymphoproliferative Patterns as Diagnostic Dilemmas in Inborn Errors of Immunity

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SUMMARY

Background. Inborn errors of immunity (IEIs) frequently manifest with lymphoproliferative disorders (LPDs) ranging from benign polyclonal hyperplasia to aggressive lymphomas. Distinguishing reactive from neoplastic LPDs is challenging due to overlapping clinical presentations, atypical histology and viral drivers, especially EBV.

Scope. This review summarizes evidence on benign and malignant LPDs in IEIs, delineating pathogenic mechanisms (genetic defects, viral oncogenesis, microenvironmental changes) and highlighting diagnostic pitfalls, including Hodgkin-like masquerades, paracortical immunoblastic proliferations, polymorphic EBV-positive lesions with clonal findings, T-cell expansions and gastrointestinal or granulomatous mimics.

Recommendations. We advocate a structured, multidisciplinary approach — comprehensive clinical and immunologic assessment, routine EBV/HHV-8 testing (EBER and quantitative PCR), excisional biopsy with detailed histology, immunophenotyping, clonality and targeted genomic analyses. Management should be individualized, balancing immune-directed therapy and targeted agents (e.g., PI3Kδ inhibitors, abatacept, sirolimus) with conventional oncologic treatment and hematopoietic stem cell transplantation when appropriate.

Conclusions. Integrated clinicopathologic and molecular evaluation, registries, and validated biomarkers are essential to improve diagnosis, guide therapy, and reduce morbidity in patients with IEI-associated LPDs.

KEYWORDS: inborn errors of immunity, IEIs, lymphoma, lymphoproliferative disorders, LPDs

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INTRODUCTION

Inborn errors of immunity (IEIs) are a heterogeneous group of genetically determined disorders that impair immune development, function, or regulation [1,2]. While recurrent and severe infections remain a signature feature, many IEIs present predominantly with immune dysregulation — namely autoimmunity, auto-/hyper-inflammation, allergy, neoplasia, and lymphoproliferation [3–5]. Lymphoproliferative disorders (LPDs) in the setting of IEIs encompass a clinical and pathologic spectrum ranging from benign, polyclonal hyperplasia to aggressive clonal lymphomas [6–9]. The same monogenic defect may manifest variably across patients and over time, producing benign and malignant lymphoid phenotypes that can be difficult to categorize [7,10]. Correct classification according to the last WHO official document (2022) has critical implications for treatment and prognosis [11], but is often hindered by unusual histologic features, atypical clinical presentations, and confounding viral triggers such as Epstein–Barr virus (EBV) [12,13].

This review aims to summarize currrent evidence on benign and malignant LPDs in IEIs, delineating pathogenic mechanisms (genetic defects, viral oncogenesis, microenvironmental changes), and highlighting diagnostic pitfalls in the field of IEI-related LPDs.

MATERIALS AND METHODS

Literature Search Strategy

A focused, comprehensive literature review was performed to identify studies, reports and guidance relevant to LPDs arising in IEIs. Searches were conducted in PubMed/MEDLINE, Scopus and Web of Science from database inception through 1 July 2025, supplemented by hand-searching of reference lists and recent review articles. Search strategies combined controlled vocabulary (e.g., MeSH terms) and free-text keywords including, but not limited to, "inborn errors of immunity", "primary immunodeficiency", "lymphoproliferative disorder", "lymphoma", "EBV", "ALPS","APDS","CVID","CTLA4", "LRBA", and "XMEN", with Boolean operators used to refine sensitivity and specificity. Searches were limited to human studies and publications in English.

Study Selection and Data Extraction, Synthesis and Analysis

Two reviewers independently screened titles and abstracts for relevance and assessed full texts against predefined inclusion and exclusion criteria. Inclusion criteria were: (1) original human studies, case series or case reports, and reviews addressing LPDs or lymphoma in the context of IEIs; (2) sufficient detail to inform diagnostic or management considerations; and (3) publication in a peer-reviewed journal. Exclusion criteria included non-human or in vitro studies, and reports lacking full data or with inadequate methodological description. Data extraction was performed independently by two reviewers. Given heterogeneity of study designs and outcomes, the synthesis was narrative and thematic, emphasizing diagnostic pitfalls, clinicopathologic correlations, and therapeutic implications rather than quantitative pooling.

Ethical Considerations

The nature of this study (a review) does not require ethical approval from an appropriate committee.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF IEI-RELATED LPDS

LPDs have been reported in many IEIs, and their frequency and histologic distribution depend on the underlying genetic defect [9,14]. Lymphoma is a common malignancy encountered in several IEI cohorts and frequently represents a leading cause of cancer-related morbidity and mortality in affected patients [15,16]. Most IEI-associated lymphomas are of B-cell lineage; however, the relative incidence of Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), marginal-zone/extranodal lymphomas, and less commonly T/Natural killer (NK)-cell neoplasms varies by syndrome [17]. Particular defects that confer high susceptibility to EBV-associated malignancy include type 1 X-linked lymphoproliferative syndrome [XLP1, SH2 Domain Containing 1A (SH2D1A) deficiency], X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia [XMEN, magnesium Transporter 1 (MAGT1) deficiency], Interleukin-2-inducible T-cell Kinase (ITK) deficiency, and CD27/CD70 pathway defects, which commonly present with fulminant EBV-driven B-cell proliferation [17]. Other disorders — such as autoimmune lymphoproliferative syndrome (ALPS), activated PI3Kδ syndrome (APDS), Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) haploinsufficiency and Lipopolysaccharide-responsive Beige-like Anchor Protein (LRBA) deficiency — frequently produce profound benign lymphoid hyperplasia, but also carry an increased long-term risk of lymphoma [3,9,18]. Common variable immunodeficiency (CVID), by virtue of its prevalence, contributes a substantial number of LPDs in adult cohorts, including granulomatous-lymphocytic interstitial lung disease (GLILD) and overt lymphoma in a minority of patients [12,19,20].

Clinically, benign LPDs present with chronic or recurrent lymphadenopathy, splenomegaly and extranodal lymphoid infiltrates (lung, liver, gastrointestinal tract) [8,21]. B-symptoms, rapidly enlarging nodes, or focal destructive lesions raise concern for transformation, but inflammatory LPDs may mimic aggressive disease both clinically, histologically, and radiologically; thus, a low threshold for tissue diagnosis is commonly required [3,7,10].

DEFINITIONS AND RED FLAGS

For practical purposes we define LPDs as persistent lymphadenopathy, hepatosplenomegaly, or lymphoid organ infiltration lasting more than 3 months, with or without chronic EBV infection, after exclusion of non-EBV infections and overt malignancy [8]. Red flags prompting evaluation for an underlying IEI include chronic or relapsing course, involvement of atypical sites (e.g., GLILD in CVID), family history of IEIs or lymphoid malignancy, concomitant autoimmune phenomena, and abnormal immunologic screening results [6,8,22].

BENIGN LYMPHOPROLIFERATION: PATTERNS AND MIMICS

Benign lymphoproliferation in IEIs includes polyclonal follicular hyperplasia, plasmacytic hyperplasia, Castleman-like histology, and polymorphous EBV-associated proliferations. Histologically these processes can be striking: massively expanded germinal centers, confluent follicles, exuberant paracortical immunoblastic proliferation, increased plasma cells, and vascular proliferation [3,7,10,23]. Activated or immunoblastic cells may express activation markers such as CD30 or Interferon Regulatory Factor 4 (IRF4) and, when EBV-positive, show strong Epstein-Barr virus-encoded small RNAs (EBER) signal, features that can closely resemble classic Hodgkin lymphoma (cHL) or EBV-positive polymorphous B-cell proliferations[3,7,10,23]. Importantly, detection of an oligoclonal or even dominant lymphocyte clone by immunoglobulin (Ig)/T cell receptor (TCR) rearrangement analysis

should be interpreted with caution in IEI patients: chronic antigenic stimulation, defective apoptosis, and homeostatic proliferation can produce clonal expansions that are not necessarily malignant [7,12].

MALIGNANT LYMPHOPROLIFERATION: HISTOLOGY, TIMING AND DRIVERS

When malignant transformation occurs, IEI-associated lymphomas most commonly include EBV-associated large B-cell lymphomas, cHL-like entities, extranodal marginal zone lymphomas, and DLBCL [15-17]. T – and NK – cell neoplasms are rarer but are characteristic of specific defects [e.g., T-cell prolymphocytic leukemia in ataxia-telangiectasia (AT) patients] [7,24].

The age of onset varies: some DNA repair disorders and severe combined immunodeficiencies (SCID) present with early childhood lymphomas, whereas APDS and ALPS patients may develop lymphoma in adolescence or adulthood [16,25]. Mechanisms underlying transformation include impaired programmed cell death (e.g., FAS pathway defects in ALPS) [26], constitutive proliferative signalling (PI3Kδ gain-of-function in APDS) [27], genomic instability [ATM deficiency in AT, NBN defects in Nijmegen breakage syndrome (NBS)] [28], and impaired EBV-specific cytotoxic responses (AT, APDS, XLP1, ITK, MAGT1, CD27/CD70 abnormalities) [17,29–32]. The interplay between intrinsic genetic susceptibility and extrinsic viral oncogenesis, within an altered microenvironment, accelerates lymphomagenesis [15].

PATHOGENESIS: HOST GENETICS, EBV AND THE MICROENVIRONMENT

The pathogenesis of LPDs in IEIs is multifactorial. Germline defects that permit survival of autoreactive or damaged lymphocytes (FAS/FASL pathway in ALPS) [26], that enhance proliferative signalling (PI3Kδ pathway in APDS) [27,32], or that impair genomic maintenance (ATM, NBN genes in AT and NBS, respectively) [28,30] lower the threshold for oncogenic transformation. EBV is a central extrinsic driver in many syndromes; the virus establishes latent infection in B cells and provides gene products that subvert apoptotic mechanisms and drive proliferation [7,13,31]. In IEIs, impaired T-cell surveillance and defective NK or cytotoxic programs allow expansion of EBV-infected clones [32]. The tumor microenvironment, especially in cHL, frequently displays prominent inflammatory infiltrates, altered T-cell subsets (including exhausted or senescent phenotypes), and variable expression of immune checkpoints, all of which modulate tumor evolution and therapeutic responses [33,34].

DIAGNOSTIC APPROACH AND PRACTICAL CONSIDERATIONS

Given the diagnostic ambiguity in many IEI-associated LPDs, a layered and multidisciplinary diagnostic strategy is required in patients with LPDs and red flags for an underlying IEI [12,28,35]. Key elements include:

- Detailed clinical assessment: age of onset, infection history (including EBV), autoimmune features, family history and organ involvement [3,36].
- Baseline immunologic workup: quantitative immunoglobulins, lymphocyte subsets with naïve/memory phenotyping, functional assays where feasible, and vaccine response assessment [3,36].
- Targeted infectious testing: EBV PCR/viral load, Cytomegalovirus (CMV)/Human Herpes Virus-8 (HHV-8) in appropriate contexts, and Human Immunodeficiency Virus (HIV) exclusion [3,7,36].
- Imaging: CT and FDG-PET/CT for staging and selection of biopsy sites, taking into account that a high Standardized Uptake Value (VUS) on PET scans is not pathognomonic of malignancy and must be interpreted, along with LPDs distribution features (e.g., symmetrical, non-symmetrical), in the IEIs context [37].
- Histopathology: excisional lymph node or core biopsy with full morphology, immunophenotyping, EBER in-situ hybridization, flow cytometry, and clonality testing (Ig/TCR rearrangement). If initial findings are equivocal, longitudinal follow-up and re-biopsy may be necessary [3,7,12].
- Genetic testing: targeted IEI panels, clinical exome sequencing, and copy number analysis should be considered early, as molecular diagnosis directly informs prognosis and therapy [3,8].
- Interpretation of clonality assays requires integration with clinical and histologic data; the presence of a clone alone should not be equated with malignancy in the absence of corroborating evidence [3,7,12].

HISTOPATHOLOGIC NUANCES AND ANCILLARY TESTING

Pathologists play a pivotal role in distinguishing reactive from neoplastic processes in IEIs. Reactive follicles generally retain polarity, tangible body macrophages and preserved mantle zones, but in IEIs these features may be distorted [12,28,35]. Immunohistochemical panels and EBER in-situ hybridization are indispensable. Molecular approaches such as next-generation sequencing (NGS) for oncogenic mutations, comprehensive repertoire sequencing, and detection of somatic copy number changes can support a diagnosis of malignancy when combined with clonal dominance and concordant histology [3,7,8,12].

DIAGNOSTIC PITFALLS

Hodgkin-like proliferations and masquerades Hodgkin-like histology in IEI can represent an extreme form of immune dysregulation rather than true neoplasia. Reed-Sternberg-like CD30+/CD15+ cells can be encountered in polymorphous EBV proliferations, mucocutaneous ulcers and paracortical expansions [7,33]. Such features have led to diagnostic reversal in reported cases [10]; for example, some CVID-associated lymphomas

have been reinterpreted as benign hyperplasia on re-review [12], the same goes for IL2RG-deficient SCID-related cHLs revisited as polymorphic B-cell proliferations [38]. Moreover, an APDS2 patient initially treated for presumed cHL was later found to have non-malignant pathology in form of a paracortical T cell expansion [39,40]. These experiences emphasize the value of integrated interpretation and, when feasible, repeating biopsy and review before exposing patients to intensive chemotherapy or hematopoietic stem cell transplantation (HSCT).

Key practical pitfalls in the setting of IEI-related LPDs, leading to malignancy misclassification, include:

- Naked germinal centers and atypical IgG/IgM patterns

Peripheral B cell hyperplasia with naked germinal centers (markedly attenuated or absent mantle zones) and aberrant IgG/IgM ratio expression skewed towards expanded IgM+ plasma cells, involving both nodal and extra-nodal sites (lungs, gastrointestinal tract, and spleen) may be a diagnostic clue to underlying IEIs, especially APDS and CVID, but can be mistaken, particularly for follicular lymphoma or marginal zone neoplasia when viewed in isolation, due to B cell expansion [3,12,33,39,40].

- Paracortical, infectious-mononucleosis-like B cell expansions

Prominent paracortical immunoblastic proliferation — frequently EBV-positive — can mimic aggressive B-cell lymphoma. Immunoblasts may express activation markers such as CD30 and show high Ki-67, creating a false impression of overt malignancy [3,7,11,13,33,38,41].

- Polymorphic EBV — positive B-cell proliferations

EBV-positive polymorphic LPDs may be clinically indolent or transient in some IEIs, yet display histologic and molecular features that are conventionally interpreted as malignant, such as tissue effacement and frequent monoclonal Ig rearrangements; therefore, detection of monoclonality should not automatically trigger cytotoxic therapy without clinicopathologic correlation and assessment of viral load and immune status [7,11,13,41].

- Diagnostic gray zones between DLBCL, cHL and T-cell-rich or Hodgkin-like patterns

In some cases DLBCL with aberrant phenotype, cHL-like lesions can be difficult to distinguish, falling into the classification of gray-zone lymphomas; in such cases, features such as sheets of blasts, sparse B-cell marker expression, or abundant histiocytes ("gray zones"), along with a careful correlation with EBV status, expression of transcription factors involved in B cell development [Paired Box 5 (PAX5), Octamer-binding Protein 2 (OCT2), B cell Octamer-binding Protein 1 (BOB.1)] and molecular findings, can guide the correct classification [23,42,43].

- Non-lymphomatous T-cell expansions and extranodal T-cell infiltrates

Nodal T-cell hyperplasia is typical of syndromes such as Omenn [44] and ALPS [45], and extra-nodal T-cell infiltrates — particularly in gut or skin — are common in CVID and leaky SCID [46,47]. Cytologic and phenotypic atypia are frequent and may prompt erroneous classification as lymphoma. Subclinical circulating T-cell clones can be detected in otherwise stable patients (including AT), and long latency cytogenetic evolution may precede frank T-cell leukemia/lymphoma by years [24,48].

Additional diagnostic pitfalls, beyond those leading to malignant misdiagnosis, include:

- Gastrointestinal mimics

IEI-associated enteritis may mimic celiac disease or idiopathic immune bowel disease (IBD); therefore, an explicit evaluation for plasma cells in duodenal biopsies (their absence argues against classical celiac disease) and vigilance for IBD-like colitis patterns across IEI subtypes are recommended. In very early-onset, treatment-refractory, or atypical presentations clinicians should consider underlying IEI [49].

- Granulomatous reactions and infectious mimics

Granulomata occur in CVID, AT, NBS and other IEIs and may be driven by infectious or post-infectious processes (including rubella vaccine strain-associated granulomas); therefore, a premature diagnosis of sarcoidosis on morphology alone when IEI is a realistic differential alternative should not be provided [46,50].

Practical recommendations include routine EBER in-situ hybridization and quantitative viral PCR, extended in select ed cases to other viral drivers (e.g., HHV-8), low threshold for excision, comprehensive immunophenotyping, and repeat sampling when needed [3,7,12,36].

We recommend concise, pathology-centerd guidance to reduce misclassification of reactive IEI-associated proliferations and to inform therapeutic decisions.

A pragmatic pocket guide for IEI-related LPD is provided in Table I.

IMAGING AND MINIMALLY INVASIVE DIAGNOSTICS

FDG-PET/CT is useful for mapping disease extent and guiding biopsy but lacks specificity for malignancy in inflammatory or autoimmune LPDs [37]. When surgical excision is impractical, image-guided core biopsies may be used, but they limit architectural assessment; tissue-conserving strategies should be weighed against the imperative to obtain diagnostic tissue [3,7,36].

MOLECULAR DIAGNOSTICS, CLONALITY AND EMERGING BIOMARKERS

High sensitivity clonality assays and immune repertoire profiling quantify clonal dynamics and may detect evolution toward dominance, which, together with the acquisition of oncogenic mutations, supports malignant progression. Circulating tumor DNA, cell-free Ig/TCR sequencing, and targeted mutation panels have potential as emerging minimally invasive diagnostic and surveillance tools to detect early transformation, but their clinical performance in IEI-associated LPDs remains under investigation [51]. Standardised thresholds, longitudinal sampling, and prospective studies are needed to validate biomarkers that stratify malignant risk.

MANAGEMENT STRATEGIES: BALANCING IMMUNE MODULATION AND ONCOLOGIC THERAPY

Therapy is dictated by disease biology, severity and patient-level considerations. For genetically determined symptomatic benign LPDs, immune-directed targeted therapies can control disease with an acceptable toxicity and a favourable risk-benefit profile, offering disease modification in term of immune dysregulation beyond lymphoproliferation: rapamycin (mTOR inhibitor) for ALPS(-like) related hyperplasias, abatacept (CTLA4-Ig) for CTLA4 haploinsufficiency or LRBA deficiency, and leniolisib (selective PI3Kδ inhibitor) for APDS [52]. For EBV-driven proliferations, rituximab may reduce B-cell reservoirs and control disease; adoptive transfer of EBV-specific cytotoxic T lymphocytes has produced durable remissions in selected contexts [23]. When definite clonal lymphoma is established, conventional oncologic protocols (chemo-immunotherapy ± radiotherapy) are generally applied with heightened attention to infection risk, comorbidity and organ reserve. HSCT remains the only curative option for many monogenic IEIs, particularly where lymphoproliferation arises from a fundamental immune defect; timing and preparative regimens must be individualized and planned by an experienced transplant team [53].

THERAPEUTIC NUANCES AND CASE-BASED CONSIDERATIONS

Clinicians must balance immune suppression against infection risk; for example, rituximab and prolonged corticosteroids aggravate hypogammaglobulinemia and susceptibility to encapsulated organisms [23,52]. Targeted agents may reduce lymphoproliferation with fewer off-target effects but require long-term safety data [52]. Cellular therapies (EBV-specific T cells, chimeric antigen receptor T cells) are promising for refractory EBV-positive or CD19+ malignancies, but the interplay with underlying immune deficiency requires expert management and infection prophylaxis [23].

FUTURE DIRECTIONS

Priority research areas include validating biomarkers predictive of malignant transformation, defining whether early targeted therapy can reduce lymphoma risk, and developing consensus diagnostic algorithms. Prospective registries and international collaboration are essential to power studies in these rare disorders.

ETHICAL AND PRACTICAL CONSIDERATIONS

Genetic counselling, family screening and discussions about pre-emptive surveillance, early therapeutic intervention or HSCT are central to care in IEI patients with LPDs. In paediatric populations, decisions must weigh curative potential against transplant risks; in adults with hypomorphic or late-onset defects, diagnostic delay is common and may adversely affect outcomes [53,54]. Multidisciplinary teams that integrate immunology, haematology/oncology, pathology and genetics provide the best framework for patient-centred decisions.

CONCLUSIONS

Conclusions and hypotheses should be firmly established/supported by the data presented, and any speculations should be clearly identified as such. No new data should be presented in the discussion.

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None.

Ethical consideration

The nature of this study (a review) does not require ethical approval from an appropriate committee.

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Conflicts of interest statement

Authors have no existing or potential conflicts of interest to disclose.

Author's contributions

Writing-Original Draft: M.M., F.C.; Writing-Review & Editing: M.M., F.C.; Conceptualization: M.M., F.C.; Data Acquisition: M.M., F.C.; Data Analysis and Interpretation: M.M., F.C. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1 Bousfiha AA, Jeddane L, Moundir A, et al. The 2024 update of IUIS phenotypic classification of human inborn errors of immunity. J Hum Immun 2025;1:e20250002. https://doi.org/10.70962/jhi.20250002.

2 Poli MC, Aksentijevich I, Bousfiha AA, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. J Hum Immun 2025;1:e20250003. https://doi.org/10.70962/jhi.20250003.

3 Sharma S, Pilania RK, Anjani G, et al. Lymphoproliferation in Inborn Errors of Immunity: The Eye Does Not See What the Mind Does Not Know. Front Immunol 2022;13:856601. https://doi.org/10.3389/fimmu.2022.856601.

4 Costagliola G, Peroni DG, Consolini R. Beyond Infections: New Warning Signs for Inborn Errors of Immunity in Children. Front Pediatr 2022;10:855445. https://doi.org/10.3389/fped.2022.855445.

5 Mauracher AA, Gujer E, Bachmann LM, et al. Patterns of Immune Dysregulation in Primary Immunodeficiencies: a Systematic Review. J Allergy Clin Immunol Pract 2021;9:792-802.e10. https://doi.org/10.1016/j.jaip.2020.10.057.

6 Hägele P, Staus P, Scheible R, et al. Diagnostic evaluation of paediatric

TABELLA I. Pocket Guide for Inborn Errors of Immunity-Associated Lymphoproliferation..

IEI (gene / syndrome)	Typical LPD phenotype(s)	Most common mimics / misdiagnoses	Key histologic clues favouring reactive *vs* malignant	Ancillary tests to perform	Clinical tip
APDS *(PIK3CD/ PIK3R1)*	Follicular hyperplasia, paracortical expansion, GLILD, plasmablast-rich lesions, nodal and extra-nodal (gastrointestinal tract, spleen) involvement	Follicular lymphoma, marginal zone lymphoma, immunoblastic lymphoma	Preserved follicular polarity in parts, abundant plasmablast, naked germinal centers with attenuated/absent mantle zone and atypical IgG/IgM pattern skewed towards IgM plasma cells expansion, T follicular helper expansion, variable CD30 expression	EBV PCR, EBER ISH, Ig clonality by PCR/ NGS, targeted NGS for somatic hits	Consider targeted PI3K-delta inhibitors (leniolisib) and discuss with immunology before cytotoxic chemotherapy
ALPS (FAS pathway defects)	Marked lymphadenopathy, splenomegaly, expanded DNT, multicentric Castleman-like pattern with nodal IgG4$^+$ plasmacell hyperplasia, nodal T cell expansion with cytological/ phenotypic atypia and clonal TCR rearrangement	Peripheral T-cell /B-cell lymphoma	Prominent sinus/follicular hyperplasia, increased DNT cells on flow, preserved architecture early	Flow cytometry for DNTs, FAS functional testing, TCR clonality	Avoid aggressive chemotherapy if immune-mediated; consider immunomodulation (sirolimus)
XLP1 *(SH2D1A)* / XLP2 *(XIAP)*	Severe EBV-driven B-cell proliferations, HLH	EBV-positive large B-cell lymphoma, HLH-associated proliferations	Polymorphic infiltrate with immunoblasts; HLH may dominate	EBV PCR, EBER ISH, immunophenotype, genetics for *SH2D1A/ XIAP*	Early HSCT consideration in fulminant cases; careful distinction between reactive EBV-LPD and lymphoma needed
CVID and CVID-like disorders	GLILD, nodular lymphoid hyperplasia, follicular hyperplasia and mixed hyperplasia with progressive transformation of germinal centers-like pattern, gut and skin Tcell infiltrates with cytological/ phenotypic atypia and clonal TCR rearrangement, duodenitis with low/absent plasma cells, skin/extra-nodal granulomas with CD8+ lymphohistiocytic infiltrates, occasional B-cell lymphoma	Follicular lymphoma, marginal zone lymphoma, cHL-like lesions (interfollicular and paracortical hyperplasia rich in reactive T cells and scattered large CD30+/CD15+ cells); coeliac disease; sarcoidosis	Granulomas, lymphoid aggregates, naked germinal centers with attenuated/ absent mantle zone and atypical IgG/IgM pattern skewed towards IgM plasma cells expansion; variable loss of normal architecture	Ig levels, vaccine response, histology + clonality, CT chest, BAL	Treat infection/ inflammation first; monitor closely before oncologic therapy; consider target therapy in monogenic forms (e.g., abatacept in CTLA4/LRBA deficiency)
DNA repair defects (***ATM***, ***NBN***)	EBV-associated proliferations in childhood, early onset B/T cell lymphoma, subclinical T cell clones with TCR rearrangement/ translocation, granulomas	Peripheral B/T cell lymphomas, T-cell prolymphocytic leukemia sarcoidosis	Rubella virus-associated skin granulomas	EBV PCR, EBER ISH, alpha-phetoprotein, immunophenotype, radiosensitivity test, genetics for *ATM/NBN*	Increased radiosensitivity and chromosomal instability. Avoid diagnostic radiation exposure

(continues)

TABELLA I *(follows).* Pocket Guide for Inborn Errors of Immunity-Associated Lymphoproliferation..

IEI (gene / syndrome)	Typical LPD phenotype(s)	Most common mimics / misdiagnoses	Key histologic clues favouring reactive *vs* malignant	Ancillary tests to perform	Clinical tip
SCID and leaky SCID (Omenn syndrome)	EBV-associated proliferations in childhood, nodal, gut and skin Tcell infiltrates with cytological/phenotypic atypia and clonal TCR rearrangement, skin/extra-nodal granulomas with CD8+ lymphohistiocytic infiltrates, occasional early-onset B-cell lymphoma	Peripheral B/T cell lymphomas; sarcoidosis	Severe immune dysregulation with mixed cellularity infiltrates; Rubella virus-associated skin granulomas	Early genetic testing for *RAG* variants, EBER ISH, clonality studies, consider functional assays	High malignancy risk in some genotypes—early HSCT evaluation

ALPS: Autoimmune Lymphoproliferative Syndrome; APDS: Activated PI3K Delta Syndrome; BAL: Bronchoalveolar Lavage; cHL: Classical Hodgkin Lymphoma; CT: Computed Tomography; CTLA4: Cytotoxic T-Lymphocyte Antigen-4; CVID: Common Variable Immunodeficiency; DNT: Double-Negative T cells; EBER: Epstein–Barr-encoded RNA; GLILD: Granulomatous-Lymphocytic Interstitial Lung Disease; HLH: Hemophagocytic Lymphohistiocytosis; HSCT: Hematopoietic Stem Cell Transplantation; IEI: Inborn Errors of Immunity; ISH: In Situ Hybridization; LPD: Lymphoproliferative Disorder; LRBA: Lipopolysaccharide-responsive Beige-Like Anchor protein; NGS: Next-Generation Sequencing; PCR: Polymerase Chain Reaction; SCID: Severe Combined Immunodeficiency; TCR: T Cell Receptor; XLP: X-linked Lymphoproliferative syndrome.

autoimmune lymphoproliferative immunodeficiencies (ALPID): a prospective cohort study. Lancet Haematol 2024;11:e114-e126. https://doi.org/10.1016/S2352-3026(23)00362-9.

7 Natkunam Y, Gratzinger D, Chadburn A, et al. Immunodeficiency-associated lymphoproliferative disorders: time for reappraisal? Blood 2018;132:1871-1878. https://doi.org/10.1182/blood-2018-04-842559.

8 Forbes LR, Eckstein OS, Gulati N, et al. Genetic errors of immunity distinguish pediatric non-malignant lymphoproliferative disorders. J Allergy Clin Immunol 2022;149:758-766. https://doi.org/10.1016/j.jaci.2021.07.015.

9 Costagliola G, De Marco E, Consonni F, et al. Inborn errors of immunity presenting with lymphoproliferation: lessons from a case series. Ann Hematol 2025;104:3117-3127. https://doi.org/10.1007/s00277-025-06456-1.

10 Kiykim A, Eker N, Surekli O, et al. Malignancy and lymphoid proliferation in primary immune deficiencies; hard to define, hard to treat. Pediatr Blood Cancer 2020;67:e28091. https://doi.org/10.1002/pbc.28091.

11 Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia 2022;36:1720-1748. https://doi.org/10.1038/s41375-022-01620-2.

12 Smith T, Cunningham-Rundles C. Lymphoid malignancy in common variable immunodeficiency in a single-center cohort. Eur J Haematol 2021;107:503-516. https://doi.org/10.1111/ejh.13687.

13 Tralongo P, Bakacs A, Larocca LM. EBV-related lymphoproliferative diseases: a review in light of new classifications. Mediterr J Hematol Infect Dis 2024;16:e2024042. https://doi.org/10.4084/MJHID.2024.042.

14 Costagliola G, Consolini R. Lymphadenopathy at the crossroad between immunodeficiency and autoinflammation: an intriguing challenge. Clin Exp Immunol 2021;205:288-305. https://doi.org/10.1111/cei.13620.

15 Hauck F, Voss R, Urban C, et al. Intrinsic and extrinsic causes of malignancies in patients with primary immunodeficiency disorders. J Allergy Clin Immunol 2018;141:59-68.e4. https://doi.org/10.1016/j.jaci.2017.06.009.

16 Herber M, Mertz P, Dieudonné Y, et al. Primary immunodeficiencies and lymphoma: a systematic review of literature. Leuk Lymphoma 2020;61:274-284. https://doi.org/10.1080/10428194.2019.1672056.

17 Riaz IB, Faridi W, Patnaik MM, et al. A Systematic Review on Predisposition to Lymphoid (B and T cell) Neoplasias in Patients With Primary Immunodeficiencies and Immune Dysregulatory Disorders (Inborn Errors of Immunity). Front Immunol 2019;10:777. https://doi.org/10.3389/fimmu.2019.00777.

18 Maccari ME, Wolkewitz M, Schwab C, et al. Activated phosphoinositide 3-kinase δ syndrome: Update from the ESID Registry and comparison with other autoimmune-lymphoproliferative inborn errors of immunity. J Allergy Clin Immunol 2023;152:984-996.e10. https://doi.org/10.1016/j.jaci.2023.06.015.

19 Yakaboski E, Fuleihan RL, Sullivan KE, et al. Lymphoproliferative Disease in CVID: a Report of Types and Frequencies from a US Patient Registry. J Clin Immunol. 2020;40:524-530. https://doi.org/10.1007/s10875-020-00769-8.

20 Moratti M, Schifino G, Baccelli F, et al. Granulomatous lymphocytic interstitial lung disease in common variable immune deficiency: an in-depth clinical, immunological, functional and radiological exploration with a focus on its management, challenged by chronic CMV infection. Front Immunol 2025;16:1589052. https://doi.org/10.3389/fimmu.2025.1589052.

21 Weiss LM, O'Malley D. Benign lymphadenopathies. Mod Pathol. 2013;26:S88-S96. https://doi.org/10.1038/modpathol.2012.176.

22 Toskov V, Ehl S. Autoimmune lymphoproliferative immunodeficiencies (ALPID) in childhood: breakdown of immune homeostasis and immune dysregulation. Mol Cell Pediatr 2023;10:11. https://doi.org/10.1186/s40348-023-00167-1.

23 Carbone A, Chadburn A, Gloghini A, et al. Immune deficiency/dysregulation -associated lymphoproliferative disorders. Revised classification and management. Blood Rev 2024;64:101167. https://doi.org/10.1016/j.blre.2023.101167.

24 Suarez F, Mahlaoui N, Canioni D, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French national registry of primary immune deficiencies. J Clin Oncol Off J Am Soc Clin Oncol 2015;33:202-208. https://doi.org/10.1200/JCO.2014.56.5101.

25 Mortaz E, Tabarsi P, Mansouri D, et al. Cancers Related to Immunodeficiencies: Update and Perspectives. Front Immunol 2016;7:365-365. https://doi.org/10.3389/fimmu.2016.00365.

26 Bleesing JJ, Nagaraj CB, Zhang K. Autoimmune Lymphoproliferative Syndrome. In: GeneReviews® [Internet]. University of Washington, Seattle, 2017. https://www.ncbi.nlm.nih.gov/sites/books/NBK1108/ (Accessed on: August 19, 2025).

27 Lucas CL, Kuehn HS, Zhao F, et al. Dominant-activating germline mutations in the gene encoding the PI(3)K catalytic subunit p110δ result in T cell senescence and human immunodeficiency. Nat Immunol 2014;15:88-97. https://doi.org/10.1038/ni.2771.

28 Bomken S, van der Werff Ten Bosch J, Attarbaschi A, et al. Current Understanding and Future Research Priorities in Malignancy Associated With Inborn Errors of Immunity and DNA Repair Disorders: The Perspective of an Interdisciplinary Working Group. Front Immunol 2018;9:2912. https://doi.org/10.3389/fimmu.2018.02912.

29 Ravell JC, Chauvin SD, He T, et al. An Update on XMEN Disease. J Clin Immunol 2020;40:671-681. https://doi.org/10.1007/s10875-020-00790-x.

30 Tatfi M, Hermine O, Suarez F. Epstein-Barr Virus (EBV)-Related Lymphoproliferative Disorders in Ataxia Telangiectasia: Does ATM Regulate EBV Life Cycle? Front Immunol 2019;9:3060. https://doi.org/10.3389/fimmu.2018.03060.

31 Farrell PJ. Epstein-Barr Virus and Cancer. Annu Rev Pathol 2019;14:29-53. https://doi.org/10.1146/annurev-pathmechdis-012418-013023.

32 Carpier JM, Lucas CL. Epstein-Barr Virus Susceptibility in Activated PI3Kδ Syndrome (APDS) Immunodeficiency. Front Immunol 2017;8:2005. https://doi.org/10.3389/fimmu.2017.02005.

33 Takahara T, Satou A, Tsuzuki T, et al. Hodgkin Lymphoma: Biology and Differential Diagnostic Problem. Diagnostics 2022;12:1507. https://doi.org/10.3390/diagnostics12061507.

34 Bertuzzi C, Righi S, Motta G, et al. Microenvironmental Traits of Classical Hodgkin's Lymphoma in Adolescents and Their Prognostic Impact. Cancers. 2024;16:4210. https://doi.org/10.3390/cancers16244210.

35 Chan JKC, Kwong YL. Common misdiagnoses in lymphomas and avoidance strategies. Lancet Oncol 2010;11:579-588. https://doi.org/10.1016/S1470-2045(09)70351-1.

36 Costagliola G, De Marco E, Massei F, et al. The Etiologic Landscape of Lymphoproliferation in Childhood: Proposal for a Diagnostic Approach Exploring from Infections to Inborn Errors of Immunity and Metabolic Diseases. Ther Clin Risk Manag 2024;20:261-274. https://doi.org/10.2147/TCRM.S462996.

37 Catelli A, Nanni C, Mulè R, et al. The Dark Side of Activated Phosphoinositide 3-Kinase-δ Syndrome 2: a Story Rewritten through FDG-PET. J Clin Med 2024;13:2203. https://doi.org/10.3390/jcm13082203.

38 Slatter MA, Angus B, Windebank K, et al. Polymorphous lymphoproliferative disorder with Hodgkin-like features in common γ-chain-deficient severe combined immunodeficiency. J Allergy Clin Immunol 2011;127:533-535. https://doi.org/10.1016/j.jaci.2010.09.036.

39 Conti F, Catelli A, Cifaldi C, et al. Case Report: Hodgkin Lymphoma and Refractory Systemic Lupus Erythematosus Unveil Activated Phosphoinositide 3-Kinase-δ Syndrome 2 in an Adult Patient. Front Pediatr 2021;9:702546. https://doi.org/10.3389/fped.2021.702546.

40 Barzaghi F, Moratti M, Panza G, et al. Report of the Italian Cohort with Activated Phosphoinositide 3-Kinase δ Syndrome in the Target Therapy Era. J Clin Immunol 2024;45:58. https://doi.org/10.1007/s10875-024-01835-1.

41 Nicolae A, Sabattini E, Ponzoni M, et al. Lymphadenitis/Reactive-Hyperplasia, Mimickers of Lymphomas, Low-Grade B-Cell Lymphomas, and Hodgkin Lymphoma. Hemato 2024;5:350-379. https://doi.org/10.3390/hemato5030026.

42 Bosch-Schips J, Granai M, Quintanilla-Martinez L, et al. The Grey Zones of Classic Hodgkin Lymphoma. Cancers 2022;14:742. https://doi.org/10.3390/cancers14030742.

43 Gibson SE, Dojcinov S, Dotlic S, et al. Mediastinal large B cell lymphoma and surrounding gray areas: a report of the lymphoma workshop of the 20th meeting of the European Association for Haematopathology. Virchows Arch Int J Pathol 2023;483:733-749. https://doi.org/10.1007/s00428-023-03550-5.

44 Rieux-Laucat F, Bahadoran P, Brousse N, et al. Highly restricted human T cell repertoire in peripheral blood and tissue-infiltrating lymphocytes in Omenn's syndrome. J Clin Invest 1998;102:312-321. https://doi.org/10.1172/JCI332.

45 Lim MS, Straus SE, Dale JK, et al. Pathological findings in human autoimmune lymphoproliferative syndrome. Am J Pathol 1998;153:1541-1550. https://doi.org/10.1016/S0002-9440(10)65742-2.

46 Ho H en, Cunningham-Rundles C. Non-infectious Complications of Common Variable Immunodeficiency: Updated Clinical Spectrum, Sequelae, and Insights to Pathogenesis. Front Immunol 2020;11:149. https://doi.org/10.3389/fimmu.2020.00149.

47 Fevang B, Fagerli UM, Sorte H, et al. Runaway Train: a Leaky Radiosensitive SCID with Skin Lesions and Multiple Lymphomas. Case Rep Immunol 2018;2018:2053716. https://doi.org/10.1155/2018/2053716.

48 Taylor AM, Metcalfe JA, Thick J, et al. Leukemia and lymphoma in ataxia telangiectasia. Blood 1996;87:423-438.

49 Velthof L, Geldof J, Truyens M, et al. Gastrointestinal Disease in Common Variable Immunodeficiency Disorder (CVID): Histological Patterns, Diagnostic Clues and Pitfalls for the Pathologist and Gastroenterologist. J Clin Med 2025;14:497. https://doi.org/10.3390/jcm14020497.

50 Buchbinder D, Hauck F, Albert MH, et al. Rubella Virus-Associated Cutaneous Granulomatous Disease: a Unique Complication in Immune-Deficient Patients, Not Limited to DNA Repair Disorders. J Clin Immunol 2019;39:81-89. https://doi.org/10.1007/s10875-018-0581-0.

51 Thomas Junior DS, Chai J, Lu YJ. The development and applications of circulating tumour cells, circulating tumour DNA and other emerging biomarkers for early cancer detection. Explor Target Anti-Tumor Ther 2025;6:1002314. https://doi.org/10.37349/etat.2025.1002314.

52 Rivalta B, Moratti M, Conti F. I disordini linfoproliferativi come espressione di immunodeficit primitivi: dalla diagnosi alla terapia mirata. Ital J Pediatr Allergy Immunol 2022;:9-16. https://doi.org/10.53151/2531-3916/2022-2.

53 Albert MH, Sirait T, Eikema DJ, et al. Hematopoietic stem cell transplantation for adolescents and adults with inborn errors of immunity: an EBMT IEWP study. Blood 2022;140:1635-1649. https://doi.org/10.1182/blood.2022015506.

54 Fox TA, Massey V, Lever C, et al. Pre-Transplant Immune Dysregulation Predicts for Poor Outcome Following Allogeneic Haematopoietic Stem Cell Transplantation in Adolescents and Adults with Inborn Errors of Immunity (IEI). J Clin Immunol 2025;45:64. https://doi.org/10.1007/s10875-024-01854-y.