Annals of Hematology (2025) 104:3117–3127
https://doi.org/10.1007/s00277-025-06456-1

REVIEW

Inborn errors of immunity presenting with lymphoproliferation: lessons from a case series

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Received: 17 February 2025 / Accepted: 9 June 2025 / Published online: 24 June 2025

Abstract

Lymphoproliferation can represent the first or leading disease sign in different inborn errors of immunity (IEI), which include autoimmune lymphoproliferative syndrome (ALPS), common variable immunodeficiency (CVID), combined immunodeficiencies, activated phosphoinositide 3-kinase δ syndrome (APDS), Epstein-Barr (EBV)-related disorders, and others. The genetic and molecular background and the clinical implications of IEI presenting with lymphoproliferation are partly unexplored. Therefore, the diagnosis and clinical management of this category of patients is particularly challenging. As treatments targeting the specific genetic defect are available for some of the IEIs associated with lymphoproliferation, identifying the molecular diagnosis is of great clinical relevance and could significantly improve the patient's long-term outcome. To this purpose, a first-level immunological assessment is strongly recommended in patients with persistent or recurrent unexplained lymphoproliferation, and specific second-level analysis can orient towards the correct clinical suspicion. The mechanisms responsible for polyclonal, benign lymphoproliferation in IEI also cause an increased susceptibility to clonal, malignant lymphoproliferation. Therefore, a careful follow-up is recommended in all the patients with IEI and polyclonal lymphoproliferation, to promptly identify the development of clonality. Moreover, as malignant lymphoproliferation can be the first disease sign of some IEI, there is increasing interest in the possibility of recognizing IEIs in patients presenting with lymphoid malignancies. This work, by describing some relevant case studies, reviews the role of lymphoproliferative features in three of the most paradigmatic conditions, particularly ALPS, CVID, and APDS, and provides an updated discussion on the diagnosis, treatment, and follow-up of patients with IEI and lymphoproliferative features.

Keywords Lymphadenopathy · Splenomegaly · Hodgkin lymphoma · Common variable immunodeficiency · Autoimmune lymphoproliferative syndrome · Activated phosphoinositide 3-kinase δ syndrome · Pediatrics

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Introduction

Lymphoproliferation, which is clinically expressed by lymphadenopathy, hepatomegaly and/or splenomegaly, or lymphoid organ infiltration, commonly results from infectious and neoplastic disorders. It can also represent one of the most common expressions of immune dysregulation in patients with inborn errors of immunity (IEI) [1, 2]. Indeed, lymphoproliferative features can be the first or leading disease sign of immune dysregulation disorders, such as autoimmune lymphoproliferative syndrome (ALPS), disorders of regulatory T cells (e.g., CTLA4 haploinsufficiency and STAT3 gain-of-function, STAT3 GOF), diseases involving a defective control of lymphocyte proliferation [1, 3] and impaired antiviral response (particularly anti-Epstein-Barr virus [EBV]) [4]. Also, primary antibody deficiencies, and particularly diseases included in the spectrum of common variable immunodeficiency (CVID), as well as several combined immunodeficiencies, may display prominent features of immune dysregulation [1, 3]. The genetic background of IEI that can present with lymphoproliferation is in continuous expansion, as well as the knowledge of their phenotypic spectrum. This often leads to an underdiagnosis or a long diagnostic latency.

In this paper, we will describe 3 of the most relevant IEIs presenting with lymphoproliferation through the discussion of paradigmatic cases, and provide a review of the main biological, diagnostic, and therapeutic implications.

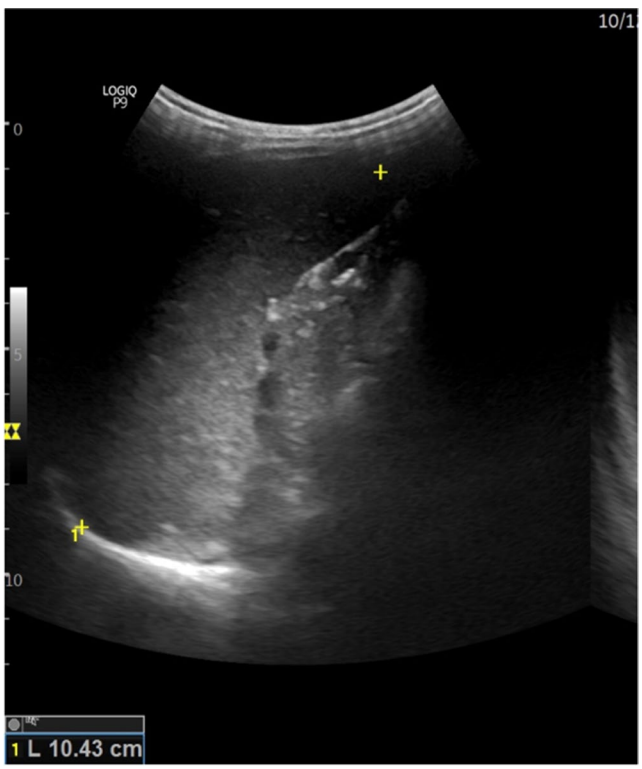


Fig. 1 Splenomegaly in an 18-month-old patient with ALPS

Autoimmune lymphoproliferative syndrome and related disorders

Case presentation

P1 is a male born from an uneventful pregnancy, with mild to moderate impairment of the main developmental milestones (speech delay) and short stature. At 18 months, he was referred to our hematology unit for hepatosplenomegaly and diffuse lymphadenopathy, first evidenced during an episode of acute gastroenteritis. At physical examination, he showed enlarged lymph nodes in the cervical, axillary, and inguinal stations, and clinically appreciable splenomegaly. Abdominal ultrasound confirmed the picture of severe splenomegaly (bipolar diameter: 10.43 cm, >99th centile for age, Fig. 1), and the lymph nodes in all the examined stations appeared enlarged (maximum diameter 3 cm in the lateral cervical station) but with conserved structure. His stature and weight were markedly reduced for age (< 3rd percentile).

Laboratory exams showed mild thrombocytopenia (platelets 90 000/uL) and hypergammaglobulinemia, with IgA 120 mg/dl (> 2 standard deviation [SD] for age), IgG 1190 mg/dl (> 2 SD), and IgM 102 mg/dl (> 1.7 SD). Diagnostic work-up for inborn errors of metabolism, including Gaucher disease, was performed and resulted negative. The immunological assessment pointed out a slight elevation of TCRαβ double-negative T cells (αβDNTs), that resulted 4% of CD3 +αβ cells associated with elevated serum vitamin B12 (> 4000 pg/ml).

Interestingly, his family history pointed out that P1's mother has been followed from the age of 4 for refractory immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA) and splenomegaly. Her previous diagnostic workup included infectious investigations, the search for autoantibodies associated with connective tissue diseases, and bone marrow aspirate with flow cytometry, which resulted negative. She received multiple treatments for ITP and AIHA, including corticosteroids and conventional immunosuppressive agents. After 2 years from disease onset, based on the refractoriness of the hematological manifestations, P1's mother underwent splenectomy, obtaining a sustained hematological improvement. An immunological assessment was never performed during the initial work-up.

At the age of 30, she presented multiple chronic cervical lymphadenopathies with elevated stiffness. She underwent two excisional biopsies, that resulted negative for infectious or neoplastic diseases. Based on the clinical presentation

of P1, also his mother underwent a clinical reassessment and laboratory immunological workup. Laboratory exams showed hypergammaglobulinemia, elevated serum B12 levels, and elevated αβDNTs (12.8% of CD3 + αβ cells, Fig. 2).

Whole exome sequencing (WES) was finally performed, showing in both the mother and P1 a pathogenic *FAS* p.A301Sfs*20 heterozygous frameshift mutation. The mutation is located in the death domain of FAS. Mutations in these domains are known to be causative of ALPS and are transmitted in an autosomal dominant fashion [5].

In P1, at the age of 2.5 years, treatment with sirolimus was initiated at 2 mg/m^2, obtaining a sustained clinical and hematological response. The platelet counts quickly normalized, while hepato-splenomegaly and lymphadenopathies dramatically reduced in terms of size. His mother refused sirolimus, and treatment with cyclosporine was initiated at the age of 32, obtaining a relevant clinical improvement. However, at 33 y/o, she developed a severe episode of sepsis, which was complicated by hemophagocytic lymphohistiocytosis (HLH). She received treatment with corticosteroids, intravenous immunoglobulins (IVIg), and intravenous antibiotics, obtaining a clinical remission of HLH.

Discussion: pathogenesis and diagnostic implications

ALPS is caused by defects in the FAS-dependent apoptotic pathway, which include mutations in *FAS*, either germline (ALPS-FAS, whose inheritance pattern depends on the site of the mutation) or somatic (ALPS-sFAS), as well as biallelic mutations in *FASL* (ALPS-FASL). More recently, germline monoallelic mutations in *FADD* with a somatic loss of heterozygosity have been associated to ALPS (ALPS-FADD) [6]. On the other hand, while variants in *CASP10* have historically been associated with ALPS, a recent study has debunked this hypothesis, stating that both homozygous and heterozygous *CASP10* variants do not give rise to ALPS [7]. Nevertheless, in a considerable percentage of patients with ALPS phenotype, a causative molecular defect remains unidentified (ALPS-U) [8, 9]. In patients with ALPS, the apoptotic defect causes an accumulation of αβDNTs and, subsequently, self-reactive T lymphocytes, thus resulting in a complex phenotype of immune dysregulation [9].

The most common clinical features of ALPS are autoimmune cytopenia (mainly, ITP) and benign lymphoproliferation [5, 8, 9]. However, patients can show other signs of autoimmunity and have a markedly higher risk of lymphoma compared to the general population, which is 40-fold higher for Hodgkin's lymphoma (HL) [8, 10]. In patients presenting with chronic or recurrent lymphoproliferation eventually accompanied by autoimmune cytopenia, specific laboratory features can significantly orient toward the diagnosis of ALPS. These include the elevation of αβDNTs, serum vitamin B12, soluble FAS-ligand (sFASL), interleukin-10 (IL-10), and IL-18, as well as the demonstration of an impaired apoptotic function [11] The elevation of these serum markers is considerably more pronounced in patients with ALPS-FAS compared to those diagnosed with ALPS-U, thus pointing out the different molecular backgrounds underlying the heterogeneity of the clinical expression of ALPS [9]. ALPS-like phenotypes (recently renamed "autoimmune lymphoproliferative immunodeficiencies, ALPID" [12]) can be observed in patients with other immune dysregulation disorders with different molecular background, such as CTLA-4 haploinsufficiency, LRBA deficiency, STAT3 GOF, and APDS [13, 14]. In a recently published large cohort of 431 patients referred for ALPID, typical ALPS was diagnosed in 16%, while other monogenic IEI in 15%, and more than 20% of the patients did not reach a definitive diagnosis [15].

In the described cases, P1 and his mother exhibited two different disease presentations. Indeed, in P1 the clinical

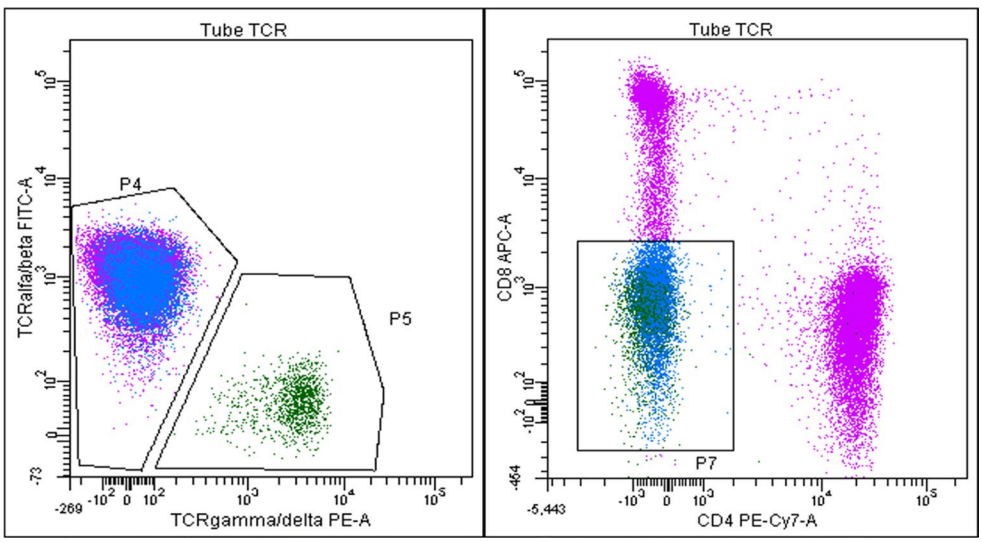


Fig. 2 Expansion of TCR αβ + double-negative T-cells in a 30-year-old patient with ALPS

phenotype at disease onset was dominated by lymphoproliferative features, while the initial disease manifestation of his mother was isolated ITP, with lymphoproliferation appearing later. In P1, the association with mild thrombocytopenia and the positive family history significantly helped to raise the diagnostic suspicion of an IEI. On the other hand, in his mother, the diagnostic delay has been considerably higher because of the non-specific disease presentation and the lack of knowledge regarding IEI at the time of disease onset. Hopefully, an increased awareness of the possibility of diagnosing IEI in patients presenting with immune dysregulation, together with the increasing availability of functional and genetic testing, will help to provide earlier recognition of ALPS and related phenotypes.

Specific warning signs to suspect ALPS/ALPID are represented by chronic or recurrent lymphoproliferation, autoimmune cytopenia– either in a single lineage [16] or bilinear [17] eventually associated with other autoimmune disorders or allergies, and positive familial history.

For what specifically concerns the genetic background of patients with chronic lymphoproliferation, a recent multicentric study by Forbes et al. demonstrated that genetic variants associated with IEI are reported in more than 50% of patients, with a higher prevalence of positive genetic testing in those <6 years old. Interestingly, patients who received a genetic diagnosis showed an increased survival rate compared to those without a molecular characterization [18]. This results from the possibility of initiating an adequate therapeutic approach based on the molecular defect [18]. In the paradigmatic case of ALPS, αβDNTs show a marked hyperactivity of mTOR-dependent molecular pathways, which is involved in their proliferative activity [19]. Therefore, sirolimus represents an effective treatment for ALPS and, potentially, other ALPID, and its use is associated with a high rate of improvement of both the lymphoproliferative features and autoimmune complications [20]. Beyond ALPS, specific targeted therapies are available for other immune dysregulation disorders classified in the ALPID spectrum, and thus potentially presenting with isolated lymphoproliferation. These options include the use of JAK-inhibitors for STAT-associated disorders (i.e., STAT3 GOF, STAT1 GOF) and the fusion protein abatacept for CTLA-4 and LRBA deficiency, thus reinforcing the importance of reaching a molecular diagnosis in this category of patients [21, 22].

The spectrum of common variable immunodeficiency

Case presentation

P2 is a patient with a previously unremarkable clinical history, who first presented to clinical attention at the age of 12 for the progressive development of bilateral cervical, inguinal, and axillary lymphadenopathies and mild splenomegaly. Ultrasound examination of the lymph nodes showed features consistent with a high suspicion of malignancy, including round morphology, absence of hilum, and peripheral vascularization. Therefore, the patient underwent inguinal lymph node biopsy, which showed follicular hyperplasia, in the absence of neoplastic infiltration. The search for EBV-encoded small RNAs (EBER) was performed and resulted negative. During the following years, the clinical picture of lymphoproliferation persisted, in the absence of other signs of immune dysregulation or relevant infectious episodes. At the age of 14, a baseline immunological assessment was performed, evidencing significant hypogammaglobulinemia, with IgA and IgG below 2 standard deviations for age (IgG 587 mg/dl, IgA 44 mg/dl), while IgM were at the lower limit (28 mg/dl, −1.9 SD) with normal B-cell count (170/mmc). Lymphocyte subpopulation analysis did not show any sign of T cell impairment. Immunoglobulin levels showed a progressive reduction during follow-up, and impaired response to tetanus was also detected. Given the picture of polyclonal lymphoproliferation, hypogammaglobulinemia with impaired specific humoral response, and absence of T cell deficiency, the patient met current diagnostic criteria for CVID. WES was performed and did not show any pathogenic variant in IEI-related genes. At the age of 21, the patient showed a marked enlargement of axillary lymph nodes, with ultrasound features consistent with malignancy. A PET scan was performed, confirming hypermetabolic features of involved lymph nodes (Fig. 3), and a subsequent lymph nodal biopsy allowed the diagnosis of CD20 +nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL). The patient was treated according to the Rituximab +CHOP (R-CHOP) scheme, obtaining a clinical remission. During follow-up the patient did not experience clinically relevant infections and after 4 years from the end of chemotherapy, he appears in good clinical conditions. However, serum immunoglobulin levels showed a further worsening, with IgG levels permanently <300 mg/dl, and the analysis of B lymphocyte subpopulations confirmed a marked reduction of CD27 +IgM-IgD- switched memory B cells (0.5%).

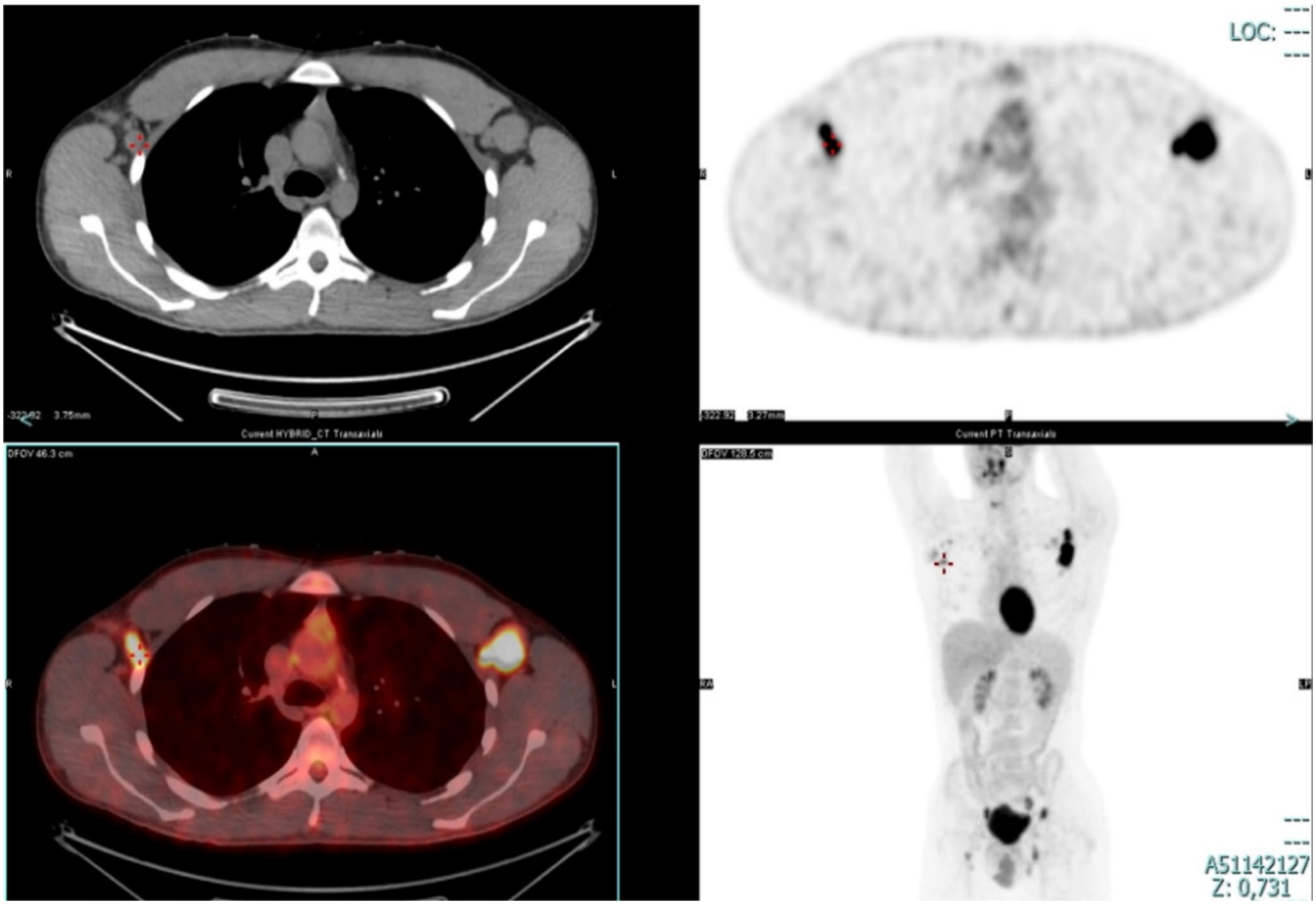


Fig. 3 PET scan findings in a patient with common variable immunodeficiency developing nodular lymphocyte-predominant Hodgkin's lymphoma (maximum standardized uptake value [SUV] of 15 in the axillary lymphadenopathies)

Discussion: inborn errors of immunity and malignant lymphoproliferation

CVID is a multifaced disease characterized by an impairment of B-cell maturation, resulting in hypogammaglobulinemia, altered germ center reactions with consequently low levels of switched memory B cells, restricted B-cell receptor (BCR) repertoire, and ineffective specific humoral response [23, 24]. Although the most common manifestations of CVID are represented by recurrent sinopulmonary infections, lymphoproliferation is described in about 15% of the patients, potentially representing the initial disease sign [25, 26]. Previous attempts to define specific genotype-to-phenotype correlations in CVID have not provided conclusive results, although it has been demonstrated that specific genetic variants, including mutations in *NFKB1* and *TACI*, are more strongly associated with lymphoproliferation [27, 28]. Moreover, patients with monogenic IEI with impaired humoral response and lymphoproliferation, such as the APDS and others, often fulfill the diagnostic criteria for CVID and present a significant clinical and laboratory overlap with this condition [27, 29, 30]. Notably, some of the mentioned conditions can present with both CVID-like and ALPID-like features (Fig. 4).

This case represents a paradigmatic example of a CVID phenotype manifesting with polyclonal and, subsequently, monoclonal lymphoproliferation. The awareness about the risk of lymphomas in patients diagnosed with IEI has increased during the last years, also following the expansion of literature data on this subject. A recent systematic review by Riaz et al. has shown that lymphomas are reported in 3–8% of patients with CVID [10]. Apart from CVID, lymphoid malignancies are described in a considerable percentage of the patients with IEI, with the highest incidence observed in EBV-related disorders (up to 50% of cases), ALPS, APDS, and disorders of regulatory T cells [10]. The mechanisms underlying the development of lymphomas in IEI are multiple and go far beyond the ineffective antitumor immune surveillance. Uncontrolled lymphocyte proliferation, defective apoptosis, altered cytokine-mediated signaling, as well as impaired DNA repair, chromosome instability, and telomere shortening contribute to oncogenesis in this category of patients [31, 32]. Concerning this, a recent study by Ye et al. has focused on the genetic

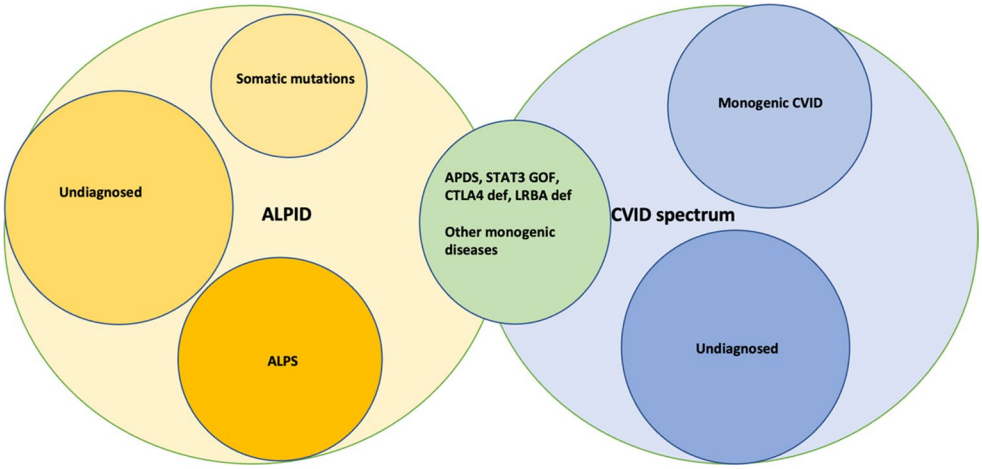


Fig. 4 An overview of IEI presenting clinical overlaps between the ALPD and CVID spectrum

characterization of lymphomas in IEI, to identify somatic mutations occurring in IEI-associated lymphomas. This study revealed that some specific patterns associated with lymphomagenesis are mutated in this category of patients, and include genes involved in apoptosis, cell cycle regulation, NKFB signaling, and DNA repair [33] although this aspect is far from being fully understood.

Because of their increased risk for malignancy, a periodical evaluation of lymphoid organs is recommended in all patients with IEI, especially in those with features of polyclonal lymphoproliferation, to promptly identify the development of clonality. Albeit specific preventive strategies are currently unavailable, the better characterization of the genomic (and, potentially, transcriptomic) pattern of IEI-associated lymphomas could potentially give rise, in the next years, to the opportunity to analyze targeted somatic panels in the tissues involved by lymphoproliferation in patients with IEI, and to finally recognize earlier those who will progress to malignancy.

Moreover, since lymphomas can be the presenting sign of an IEI, it is crucial to enhance the identification of possible IEIs in patients who first come to medical attention either with a suspicion or a confirmed diagnosis of malignancy [10, 34, 35].

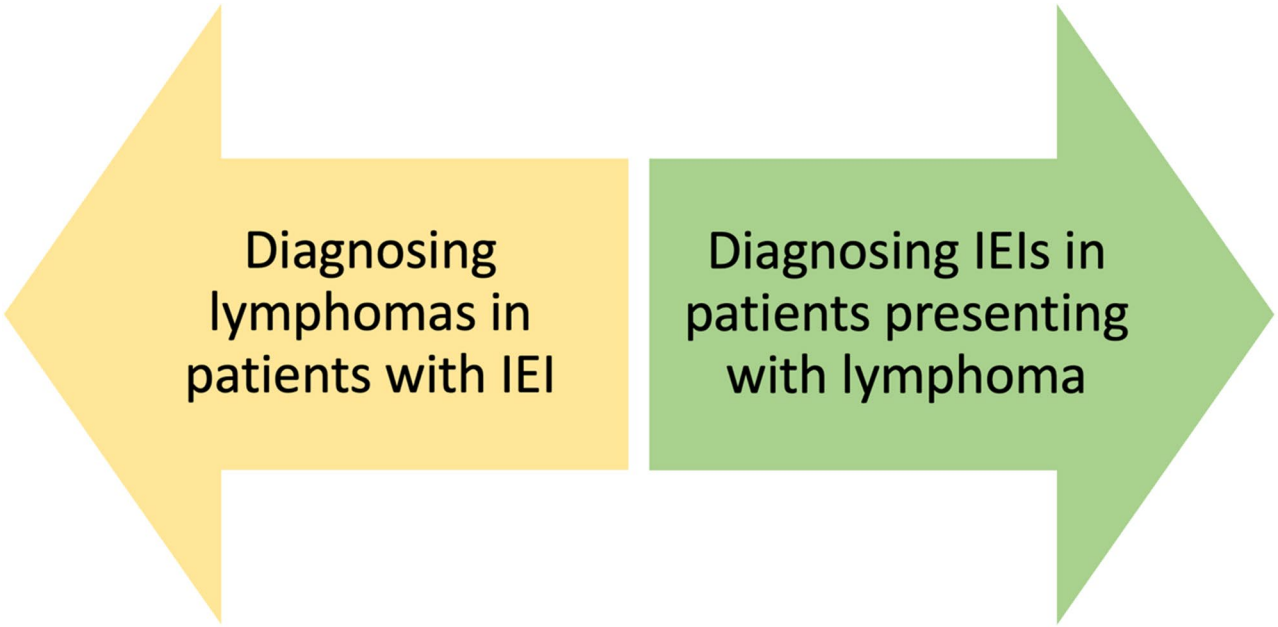
Current recommendations suggest evaluating all pediatric and adolescent patients with cancer to reveal those at higher risk of an underlying IEI. Patients have to be screened for a personal history of recurrent or severe infections, signs of immune dysregulation, syndromic features, and developmental delay, while familial history should be focused on the presence of other cases of malignancies, IEI, or autoimmune diseases [3, 36, 37]. Notably, the highest risk for IEI has been established for patients presenting with neoplasia associated with viral infections (i.e. EBV-associated lymphomas or soft tissue tumors, HPV-associated cancers) [10, 36].

Regarding lymphomas specifically, since they are the most observed type of cancer in IEI, there is a uniform agreement to perform a baseline immunological assessment at disease onset, including the analysis of serum immunoglobulin levels and lymphocyte subsets. However, as this could identify only a limited number of patients with specific conditions, such as ALPS, CVID, and others, it is reasonable to suggest the use of a more detailed immunological work-up (including the analysis of extended lymphocyte phenotyping), and eventually genetic analysis, for patients with lymphoma carrying the above-indicated signs of high clinical suspicion of IEI (Fig. 5).

Activated phosphoinositide 3-kinase δ syndrome

Case presentation

P3 is a female patient who first presented to clinical attention for the development of diffuse lymphadenopathies at the age of 8 years, in the absence of hepatomegaly or splenomegaly. Her past medical history revealed recurrent respiratory infections, not requiring hospitalization, and recurrent episodes of parotitis that were treated with multiple cycles of oral antibiotics. No other manifestations of immune dysregulation were reported. Lymphadenopathy presented a chronic-relapsing disease course, but the patient was not further investigated. At the age of 13, she underwent endocrinological assessment for short stature and delayed puberty. On this occasion, clinical examination highlighted diffuse cervical, axillary and crural lymphadenopathies, enlarged parotid glands, and severe hepatosplenomegaly. Therefore, she was addressed to hematological evaluation. US confirmed these clinical findings, with a maximum lymph node diameter of 6.5 cm in the periumbilical area. Lymph nodes appeared round, anechoic, and inhomogeneous. An



Clinical practice	Perspectives
Periodical clinical and laboratory assessment	Identifying immunopenotypic features associated with clonal LPD
US assessment in patients with LPD	Characterizing patterns of somatic mutations predicting clonal PLD
Close monitoring for patients with specific genetic risk of malignant LPD	

Clinical history	Physical and first-level assessment
Family history of lymphoma	EBV-associated lymphoma
Family history of immune dysregulation	Hypogammaglobulinemia
Consanguineous kindred	Altered conventional lymphocyte subsets
Personal history of severe/recurrent infections	Bronchiectasis
Personal history of immune dysregulation, enteropathy	Short stature, syndromic features developmental delay

Fig. 5 Warning signs for the diagnosis of an underlying IEI in patients presenting with lymphoma and red flags for the early identification of lymphoproliferative diseases in patients with IEI

extended laboratory work-up was performed and was negative for acute infections but revealed lymphopenia (total lymphocytes: 1270/mmc with low CD4/CD8 ratio [0.57]: 435/mmc total CD4 +and 765/mmc total CD8+) and reduced CD19 +cells (5% of lymphocytes), elevation of inflammatory markers and serum vitamin B12, and hypergammaglobulinemia (IgG 2056 mg/dl). Direct antiglobulin test (DAT) was positive, without clinical signs of hemolysis. The patient underwent lymph node biopsy, which showed follicular hyperplasia, negative EBER and no signs of malignant transformation. Bone marrow aspirate and biopsy showed a high prevalence of small, mature T CD3 +cells, but no signs of malignant infiltration. In the suspicion of an underlying IEI, the analysis of the extended lymphocyte phenotyping was performed and revealed a marked expansion of CD38 +CD24 transitional B cells (42.7% of CD19 +cells) and CD27 +IgM- IgD- switched memory B cells (30.3% of CD19 +cells), associated with a slight elevation of αβDNTs (2.4% of total lymphocytes). WES finally allowed the identification of a *de novo* pathogenic variant in *PI3KCD* (c.1574 A> C), resulting in the diagnosis of APDS.

Regarding treatment, it should be considered that, at the time of this case, specific PI3K inhibitors were not available. Therefore, at the age of 14, the patient started treatment with sirolimus at 2 mg/m^2, with partial remission of the clinical phenotype. During follow-up, she developed multiple respiratory infections and a severe episode of pneumonia, which led to withdrawal of sirolimus. Given the high risk of developing clonal lymphoproliferation and the high infectious burden, a decision was made to perform HSCT, given the availability of a matched unrelated donor. The conditioning regimen consisted in fludarabine and treosulfan. The patient also received serotherapy with anti-thymocyte globulin, rituximab for the prophylaxis of post-transplant lymphoproliferative disorder, and graft-versus-host disease prophylaxis with cyclosporine and methotrexate. She achieved a successful engraftment, and after 5 years from HSCT the patient is in good clinical conditions, with full donor chimerism, and has not experienced relevant infections or disease relapses.

Discussion: APDS as a paradigm of the new therapeutic implications for IEIs presenting with lymphoproliferation

APDS is an IEI situated at a crossroad between antibody deficiency and immune dysregulation. It is caused by mutations enhancing the activation of the PI3K-dependent pathways, which include GOF mutations of the catalytic subunit δ (APDS1) and loss-of-function of its regulatory subunit 1 (APDS2) [38]. The molecular defects determine a secondary activation of several intracellular pathways, including mTOR-dependent signaling, causing excessive lymphocyte activation and proliferation [39] and a loss of B-cell tolerance with enhanced autoantibody production [40].

APDS can clinically present with an infectious phenotype, consisting of an increased risk of sinopulmonary infections and herpesvirus infections, but also with prominent signs of immune dysregulation, with lymphoproliferation and autoimmune cytopenia being the most frequently observed features [38, 41–44]. The finding of dysgammalgobulinemia and the evidence of a high lymphocyte proliferation rate, demonstrated by the increase of senescent T CD8 +cells (i.e., CD3 +CD8 +CD57 +cells) and transitional B cells play an important role in recognizing APDS [38, 45, 46]. In the described case, although the patient presented with a clinical picture dominated by massive lymphoproliferation, the previous history of infections (recurrent respiratory infections and parotitis) raised suspicion of an IEI. Abnormalities in the first-level lymphocyte phenotyping, such as B-cell lymphocytopenia, as well as the slight elevation of ALPS-associated markers, finally led to performing an extended immunological assessment and genetic testing. Apart from serum markers, the histological characterization of lymph nodes of patients who have been referred for chronic lymphoproliferation can be helpful to orient towards a diagnosis of IEI. Indeed, although specific histologic patterns for the single IEI have not yet been defined, some findings that are more typically associated with IEI (i.e. granulomatous disease, massive follicular hyperplasia, germ center disruption) can lead to performing an immunological assessment [1, 47–49].

Other consideration could be made regarding the treatment choice in this patient. Indeed, although most of the patients with IEI featured by prominent immune dysregulation recognize HSCT as the only definitive treatment, in some peculiar cases, specific agents targeting the molecular defects responsible for lymphoproliferation and autoimmunity in IEI are currently available. Concerning APDS, there is uniform experience with the use of sirolimus, but recently specific PI3K inhibitors (i.e. leniolisib, nemiralisib) have been introduced [50, 51]. The use of leniolisib has shown a reduction in the infectious rate, need for immunoglobulin replacement, and lymphoproliferative features in patients with APDS, in association with good tolerability in terms of adverse events [52]. However, long-term follow-up data are needed to assess the persistence of a clinical and laboratory response to leniolisib and to better define the safety profile in a long-term setting. Also, data on HSCT in APDS are limited. According to a recent systematic review, overall mortality after HSCT in APDS is 15.6%, with the leading cause of death being lymphoma (overall mortality of 47.6%) [53]. A large international cohort study on 57 patients reported a similar overall mortality rate after HSCT and a 18% incidence of graft failure [54]. Moreover, the two approaches–targeted therapy and HSCT– could be interconnected, meaning that leniolisib/sirolimus could be used as a bridge therapy to HSCT and gradually tapered during the transplant process. Further prospective studies are needed to optimize the medical approach to APDS, and, given its rarity, a large international effort is required to establish common treatment and transplant protocols.

Conclusions future perspectives

This case series deals with an important issue regarding the need to increase awareness about the potential diagnosis of IEI in patients presenting with unexplained persistent or recurrent lymphoproliferation. The availability of specific targeted treatments for certain conditions, along with the need for adequate lymphoma surveillance, underscores the importance of an accurate clinical and molecular diagnosis. In the diagnostic approach, a personal history of recurrent or severe infections, autoimmune diseases (hematologic, cutaneous, endocrinological), growth delay, or a positive familial history of autoimmunity, lymphoproliferation, or lymphoid malignancy should alert the clinician toward the possibility of an underlying IEI [3].

These elements, together with the result of a first-level laboratory assessment, can also be helpful to reveal patients at risk for IEI among those presenting with lymphomas. The analysis of peripheral blood count, serum immunoglobulin levels, lymphocyte subpopulation, αβDNTs, and vitamin B12, which should be performed during the initial workup, can finally help in identifying selected patients with high clinical suspicion of IEI, in which the evaluation of extended B and T cell phenotyping, switched memory B cells, senescent T cells, specific humoral response, serum cytokines (e.g., IL-10, IL-18), and apoptotic function assay could provide elements useful to help in addressing the patient to adequate genetic testing (Sanger sequencing, panel NGS, WES, whole genome sequencing, CGH array) [37]. Indeed, although there is a significant clinical overlap between the different IEI that can present with lymphoproliferative

features [55] and most of the patients are finally addressed to dedicated sequencing panels, some specific clinical and laboratory patterns can orient towards a definite diagnosis and allow specific genetic testing.

Hopefully, a better characterization of the genetic and molecular background of IEI associated with lymphoproliferation could help in providing an earlier diagnosis of IEI and in obtaining an adequate target. In conclusion, in the widening galaxy of IEI, where new IEI-associated genes and new IEI phenotypes are increasingly being discovered [56] lymphoproliferation could be the first clue.

Acknowledgements This study was supported in part by funds from the "Current Research Annual Funding" of the Italian Ministry of Health.

Author contributions G.Co., G.C. and R.C. conceived the study. G.Co., E.D.M., V.R. and F.C. wrote the main manuscript text. G.Co., E.D.M. and A.L. prepared figures. E.G., C.M., G.Ca. and R.C. critically revised the text. All authors reviewed the manuscript and approved its submission.

Funding This study was supported in part by funds from the "Current Research Annual Funding" of the Italian Ministry of Health.

Data availability Data is provided within the manuscript.

Declarations

Ethics statement The patient, or their parents in the case of minors, provided consent for the publication of the manuscript.

Competing interests The authors declare no competing interests.

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