

REVIEW

Lymphadenopathy at the crossroad between immunodeficiency and autoinflammation: An intriguing challenge

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Abstract

Lymphadenopathies can be part of the clinical spectrum of several primary immunodeficiencies, including diseases with immune dysregulation and autoinflammatory disorders, as the clinical expression of benign polyclonal lymphoproliferation, granulomatous disease or lymphoid malignancy. Lymphadenopathy poses a significant diagnostic dilemma when it represents the first sign of a disorder of the immune system, leading to a consequently delayed diagnosis. Additionally, the finding of lymphadenopathy in a patient with diagnosed immunodeficiency raises the question of the differential diagnosis between benign lymphoproliferation and malignancies. Lymphadenopathies are evidenced in 15–20% of the patients with common variable immunodeficiency, while in other antibody deficiencies the prevalence is lower. They are also evidenced in different combined immunodeficiency disorders, including Omenn syndrome, which presents in the first months of life. Interestingly, in the activated phosphoinositide 3-kinase delta syndrome, autoimmune lymphoproliferative syndrome, Epstein–Barr virus (EBV)-related lymphoproliferative disorders and regulatory T cell disorders, lymphadenopathy is one of the leading signs of the entire clinical picture. Among autoinflammatory diseases, the highest prevalence of lymphadenopathies is observed in patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) and hyper-immunoglobulin (Ig)D syndrome. The mechanisms underlying lymphoproliferation in the different disorders of the immune system are multiple and not completely elucidated. The advances in genetic techniques provide the opportunity of identifying new monogenic disorders, allowing genotype–phenotype correlations to be made and to provide adequate follow-up and treatment in the single diseases. In this work, we provide an overview of the most relevant immune disorders associated with lymphadenopathy, focusing on their diagnostic and prognostic implications.

KEYWORDS

activated phosphoinositide 3-kinase δ syndrome, autoimmune lymphoproliferative syndrome, common variable immunodeficiency, CTLA-4, LRBA

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INTRODUCTION

Lymphadenopathy can be part of the clinical spectrum of different primary immunodeficiency disorders (PIDs), including diseases with immune dysregulation, and auto-inflammatory disorders. In these conditions, the altered immune or inflammatory function can be responsible for a polyclonal lymphoproliferation presenting with lymphadenopathy, hepatosplenomegaly or peripheral lymphocytosis. Lymphadenopathy and other clinical features of lymphoproliferation can represent the first clinical presentation or the leading sign of immune disorders, causing frequent misdiagnosis with hematological malignancies and delayed diagnosis [1,2]. It is relevant to note that immune diseases themselves, particularly if associated with benign lymphoproliferation, also show an increased risk of lymphoid malignancies, and [3] therefore the presence of lymphadenopathy in patients with a diagnosis of PID can be difficult to interpret.

Knowledge of the multiple molecular mechanisms underlying lymphoproliferation in immune disease has been rapidly progressing, together with the identification of new monogenic forms of PIDs, through the use of next-generation and whole-exome sequencing techniques [4,5].

In this paper, we review the genetic background, the clinical pictures and laboratory features of the most relevant

disorders of the immune and inflammatory response associated with lymphadenopathy, including those characterized by immune dysregulation and defects of innate immunity (Figure 1). Moreover, we describe the main warning signs to guide the diagnostic approach and prognostic implications, including the risk either of extranodal disease or malignancies in each condition.

Lymphadenopathies in T and B cell immunodeficiencies

Among primary antibody deficiencies, the most significant prevalence of lymphadenopathy is reported in patients with common variable immunodeficiency (CVID), while it is described with lower frequency in patients with other disorders, including X-linked agammaglobulinemia (XLA), hyper-immunoglobulin (Ig)M syndrome (HIGM) and selective IgA deficiency (Figure 2).

Primary antibody deficiencies

CVID is defined by the presence of clinical signs (increased risk of infection, immune dysregulation with

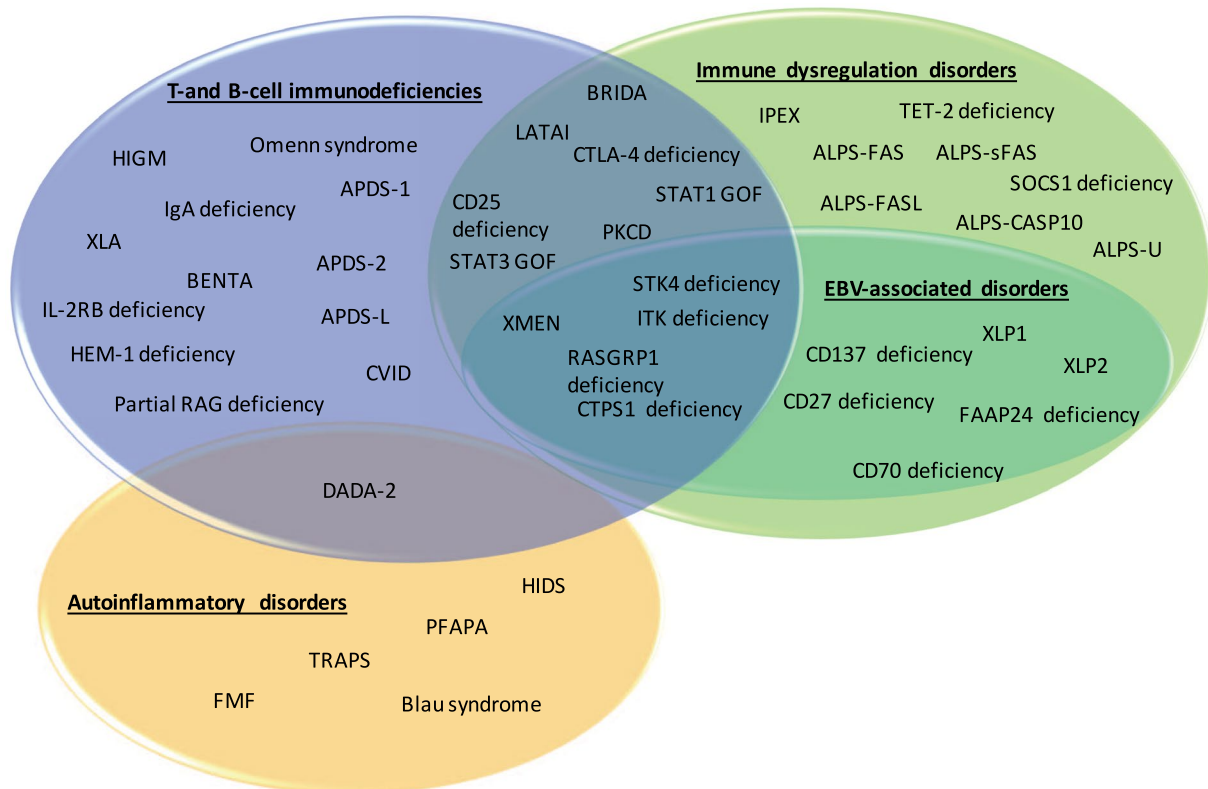


FIGURE 1 Immunodeficiency, immune dysregulation and autoinflammatory disorders associated with lymphadenopathy. The figure shows the classification of primary immunodeficiency disorders associated with lymphadenopathy, including immune dysregulation and autoinflammatory disorders. In particular, the significant overlap between T and B cell immunodeficiency and immune dysregulation disorders is highlighted

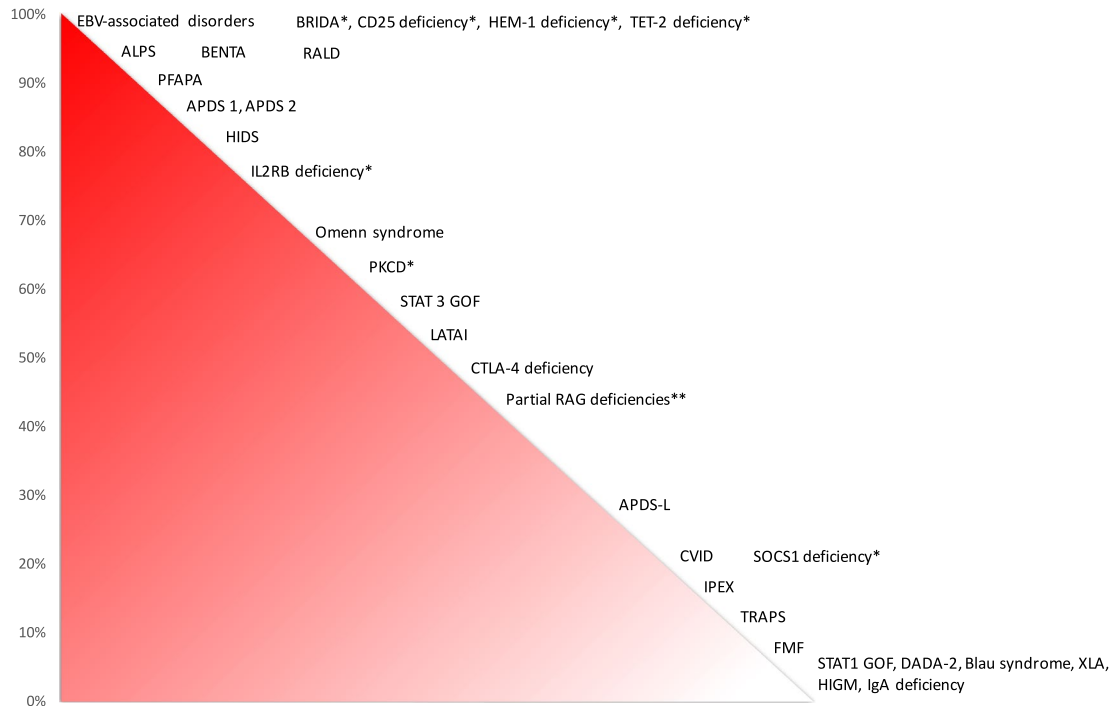


FIGURE 2 Frequency of lymphadenopathy in immunodeficiency, immune dysregulation and autoinflammatory disorders. *Fewer than 10 described patients. **Highly variable clinical phenotype

autoimmunity, lymphoproliferation, granulomatous disease) accompanied by a reduction of two immunoglobulin isotypes and poor response to vaccinations or reduced switched-memory B cells, in the absence of a T cellular deficiency, where other causes of hypogammaglobulinemia have been excluded [6]. Patients with CVID can develop lymphadenopathies at disease onset or during the clinical course as the clinical expression of benign polyclonal lymphoproliferation, granulomatous disease phenotype or lymphoma [7]. In a significant percentage of patients, the involvement of lymph nodes precedes the other clinical features of CVID [8], complicating and delaying the diagnostic process. Overall, lymphoproliferation has been reported to occur in 15–20% of patients [9–11], with splenomegaly and lymphadenopathy being frequently associated [12]. The pathogenesis of lymphoproliferation in CVID is not completely elucidated, and the role of genetic background and immunological features is currently being investigated [9,13]. Although a clear genotype–phenotype association is not demonstrated, nuclear factor kappa B1 (NF- κ B1) and transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor (TACI) mutations seem to be related to the development of lymphoproliferation and autoimmunity, with NF- κ B1 mutation being the most common molecular defect observed in a large cohort of CVID patients with lymphoproliferation [14,15]. Concerning the immunological parameters, it emerges that in patients with benign lymphoproliferation a significant expansion of transitional B cells is common

[12]. Additionally, a relationship between lymphoproliferation and preserved IgM levels has been suggested [9,10].

Granulomatous disease, featured by non-caseating and sterile granulomas in different systems, is described in 8–22% of the patients with CVID and typically affects the lungs, spleen, lymph nodes and skin [16]. Moreover, granulomas can be detected in the liver, bone marrow, kidney, brain, gastrointestinal tract, eye and parotid glands [17]. Granulomatous CVID is more frequently diagnosed in patients with lymphoproliferation, being strongly associated with the presence of splenomegaly [12], suggesting a common pathogenic mechanism between the two disease phenotypes. Accordingly, recent studies have revealed that patients with the granulomatous disease have a marked reduction of switched-memory B cells and IgM-only memory B cells, which can also be observed in patients with lymphoproliferation (particularly those with splenomegaly) [18].

The finding of lymphadenopathy in patients with CVID carries significant clinical and prognostic implications. They have an increased susceptibility to the development of both nodal and extranodal lymphomas, particularly non-Hodgkin's lymphomas (NHL), which is reported in 4% of the patients [19] (Table 1). The risk of lymphoid neoplasms is higher in CVID patients with other features of lymphoproliferation [9,19,20], thus highlighting the need of an accurate diagnostic approach to lymph node enlargement in this disease. Although most lymphadenopathies in CVID are benign [11], in the absence of adequate non-invasive predictors of malignancy the finding of lymphadenopathy often requires

TABLE 1 Risk of lymphoid and non-lymphoid malignancies in primary immunodeficiency disorder

Disease	Risk of malignancies
CVID [3,19]	3–8% of the patients develop HL or NHL. Increased risk of MALT-associated lymphomas Increased risk of gastric cancer and breast cancer
XLA [25,26]	Overall 1.5–6% risk of malignancy. Increased risk of NHL and gastrointestinal malignancies
RAG deficiency [34]	Reports of T cell lymphoma
APDS-1, APDS-2 [42]	Lymphomas (> NHL) reported in 13–28% of the patients Reports of breast cancer, rhabdomyosarcoma, basal cell carcinoma
APDS-L [46]	Increased risk for multiple non-lymphoid neoplasms (the breast, thyroid, endometrium, colon and others)
ALPS [55,56]	51-fold increased risk for HL, 14-fold increased risk for NHL
CTLA-4 deficiency [70]	17% of the patients develop lymphomas (> HL) Increased risk of gastric cancer
LATAI [70]	7% of the patients develop lymphomas (HL, NHL)
STAT3 GOF [77]	Reports of HL [1] and leukemia [1] Reports of squamous cell carcinoma
STAT1 GOF [79]	Reports of HL [2]
SOCS1 deficiency [80]	Report of HL [1]
TET2 deficiency [60]	NHL (2 B cell NHL, 1 T cell NHL) reported in all 3 described patients
XLP-1 [99,100]	Lymphoma (mainly B cell NHL) reported in up to 50% of the patients
XMEN [94]	EBV-associated lymphoma (> HL) reported in 12 of 36 of the described patients Report of Kaposi sarcoma [1]
STK4 deficiency [88]	Lymphoma (HL, NHL) reported in three of 15 of the described patients
ITK deficiency [3,84]	EBV-related lymphomas reported in 13 of 18 of the described patients (> HL) Reports of smooth muscle tumor [1] and epidermodysplasia verruciformis [2]
CD70 deficiency [93]	Lymphoma (> HL) reported in up to 50% of the described patients
CD27 deficiency [93]	Lymphoma (> HL) reported in up to 40% of the described patients
CTPS1 deficiency [84]	B cell NHL reported in two of 18 described patients
CD137 deficiency [87]	HL reported in one of the two described patients
RASGRP1 deficiency [3,84]	Lymphomas reported in up to 50% of the described patients (B cell NHL, HL)
RALD [53,54]	Reports of NHL
WAS [48]	3–12% risk of lymphoma (HL, NHL)
AT [51]	25% lifetime risk of malignancies, mostly NHL Increased risk of breast, liver and gastrointestinal neoplasms
NBS [49]	40% of the patients develop malignancies by the age of 20 years, mostly NHL Reports of HL, acute lymphoblastic leukemia, acute myeloblastic leukemia Increased risk for other malignancies, including brain tumors and rhabdomyosarcoma
Bloom syndrome [50]	25% lifetime risk of malignancies, mostly leukemia and lymphomas (15%) 16% of the patients develop skin cancers Increased risk of breast, colorectal and laryngeal cancer
CHH [52]	Up to 40% of the patients develop malignancies by the age of 65 (mainly HL) Higher risk of skin cancers

Abbreviations: ALPS = autoimmune lymphoproliferative syndrome; APDS = activated phosphoinositide 3-kinase δ syndrome; APDS-L = activated phosphoinositide 3-kinase δ syndrome-like; AT = ataxia-teleangiectasia; CHH = cartilage-hair hypoplasia; CTLA-4 = cytotoxic T lymphocyte antigen-4; CTPS1 = CTP synthase 1; CVID = common variable immunodeficiency; EBV = Epstein-Barr virus; GOF = gain-of-function; HEM-1 = hematopoietic protein 1; HL = Hodgkin's lymphomas; ITK = interleukin-2-inducible T cell kinase; LATAI = LRBA deficiency with autoantibodies, regulatory T cell (T_{reg}) cell defects, autoimmune infiltration and enteropathy; NBS = Nijmegen breakage syndrome; NHL = non-Hodgkin's lymphomas; RAG = recombinase activating genes; RALD = RAS-associated autoimmune leukoproliferative disease; RASGRP1 = RAS guanyl-releasing protein 1; SOCS1 = suppressor of cytokine signaling 1; STAT = signal transduced and activator of transcription; STK4 = serine/threonine kinase 4; TET-2 = 10–11 translocation methylcytosine dioxygenase 2; WAS = Wiskott-Aldrich syndrome; XLA = X-linked agammaglobulinemia; XLP = X-linked proliferative syndrome; XMEN = X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia.

performing a lymph-nodal biopsy, the interpretation of which could be complicated by the variable degree of histological alterations observed in benign lymph nodes of CVID patients [21]. Indeed, although the most common histological finding is lymphoid hyperplasia with reduced plasma cells, some patients can show disrupted germinal centers and a clonal expansion in non-malignant lymph nodes, potentially mimicking lymphomas [20]. Moreover, patients with CVID and lymphoproliferation or granulomatous disease have a higher risk of developing pulmonary involvement, described as 'granulomatous lymphocytic interstitial lung disease' (GLILD), which is responsible for significant mortality in these patients [22]. GLILD is frequently misdiagnosed as sarcoidosis, but a correct diagnosis is mandatory to provide adequate immunosuppressive treatment. Currently, azathioprine, mycophenolate mofetil and rituximab are the most widely used medications for GLILD [23].

Differently from CVID, benign lymphoproliferation is not part of the classical clinical picture of XLA, although it has been described in a reduced number of patients [24]. Consequently, in patients with XLA the finding of lymphadenopathy should alert the clinician regarding the high risk of neoplastic disease, including NHL and gastrointestinal neoplasia, which are reported with increased frequency in this disease [3,25,26]. Concerning HIGM, the association between infections and polyclonal lymphoproliferation is more commonly reported in patients with activation-induced deaminase (AID) or uracil-DNA glycosylase (UNG) mutations, in which the molecular defect impairs the class-switch recombination and somatic hypermutation [27].

Combined immunodeficiencies

Lymphadenopathy can be part of the clinical picture of several diseases classified among the group of combined immunodeficiency disorders (CID), including conditions that share common features with immune dysregulation disorders (Table 2) [4,28].

In young infants, the finding of features of lymphoproliferation (commonly hepatosplenomegaly, but lymphadenopathies are also reported) in the context of a suspected PID strongly suggests the diagnosis of Omenn syndrome (OS), a subtype of severe combined immunodeficiency disorder (SCID) featured by the peripheral expansion of oligoclonal T cells, which is most frequently caused by mutations of the recombinase activating genes 1 and 2 (RAG 1 and RAG 2) [29]. Other molecular defects [mutations of adenylate kinase 2 (AK2), Janus kinase 3 (JAK3), interleukin 7 receptor (IL7R) genes and others] have been associated with the clinical picture of OS, although in rare cases [30]. In OS, the susceptibility to infections is accompanied by severe eczema (caused by skin infiltration of eosinophils, lymphocytes and

histocytes), lymphadenopathy and hepatosplenomegaly [31]. Laboratory findings include peripheral eosinophilia, usually accompanied by absent circulating B cells and elevation of serum IgE [31]. Similarly to the other SCIDs, it is known that patients with OS, unless promptly initiated for hematopoietic stem-cell transplantation (HSCT), die in early life from severe infections [32].

Benign lymphoproliferation is described with considerable frequency in other rare monogenic CIDs (Table 2). Partial mutations of RAG genes have marked genetic and clinical heterogeneity, which is far from being fully understood and can be responsible for a clinical picture of combined immunodeficiency associated with immune dysregulation, lymphadenopathy, hepatosplenomegaly and granulomatous disease [33]. In patients with RAG-dependent immunodeficiency, the risk of lymphoid malignancies, and particularly NHL, is higher compared to the general population [29,34]. The histological finding of granulomas is of relevance in the diagnostic process. Notably, in some patients with partial RAG deficiency, the rubella virus vaccine strain has been detected in granulomas [35]; therefore, testing for rubella in the histological specimen could provide further help in the diagnostic approach. Another useful diagnostic tool is represented by the study of T cell receptor (TCR) variability, diversity and joining [V(D)J] recombination through V α 7.2 analysis with fluorescence-activated cell sorting (FACS), which significantly helps to differentiate RAG deficiencies from other CIDs [36].

The prevalence of lymphadenopathy, both as a presentation sign and during the clinical course, is highly relevant among the diseases caused by mutations in the caspase recruitment domain family member 11-B cell lymphoma/leukemia 10-mucosa-associated lymphoid tissue lymphoma translocation protein 1 (CARD11-BCL10-MALT1) molecular complex [37], including B cell expansion with NF- κ B and T cell anergy (BENTA), deriving from gain-of-function (GOF) mutations of CARD11 [38].

Although extremely rare, mutations of the IL-2 receptor β chain (IL-2RB) gene and hematopoietic protein 1 (HEM-1) deficiency are also associated with complex clinical phenotypes, including lymphadenopathy, autoimmune manifestations and enhanced inflammation (Table 2) [39,40].

Activated phosphoinositide 3-kinase δ syndrome and related disorders

The activated phosphoinositide 3-kinase δ syndrome (APDS), a recently described autosomal-dominant primary immunodeficiency associated with lymphoproliferation and autoimmunity, represents a paradigmatic condition. The disease is caused by mutations in the molecular complex of the phosphoinositide 3-kinase (PI3K), particularly

TABLE 2 Genetic background of combined immunodeficiencies associated with lymphadenopathies and clinical implications

Disease	Molecular defect	Other clinical features and implications	Main laboratory findings
Omenn syndrome [29–31]	Mutation of the RAG genes cause altered VDJ recombination	Life-threatening infections in the first months of life Splenomegaly, hepatomegaly, generalized erythroderma	↑ Peripheral eosinophils, serum IgE
	Other molecular defects reported: mutations of AK2, JAK3, IL-7R.		↓ Circulating B cells, TRECs in neonatal screening
RAG-associated disorders [29,33,34]	Mutation of the RAG genes cause altered VDJ recombination	Splenomegaly, hepatomegaly, susceptibility to viral and bacterial infections, autoimmune cytopenia, organ-specific autoimmunity	↓ Peripheral lymphocytes, impaired T cell function
		Granulomas in skin, mucosae, solid organs. GLILD	Hypogammaglobulinemia/ HIGM
BENTA [37,38]	Gain of function mutation of CARD11, leading to over activation of the NF-κB pathway	Splenomegaly. Recurrent sinopulmonary infections. Increased risk of viral infections (herpesviruses)	↑ Peripheral lymphocytes, B CD19 cells; ↓ Memory B cells, class-switched B cells Hypogammaglobulinemia
IL-2 Rβ deficiency [39]	IL-R2B mutation causes reduced STAT-5 activity and a reduced expansion of T _{regs}	Combined immunodeficiency; bowel inflammation, dermatological abnormalities, endocrinopathy. Susceptibility to herpesvirus infections (cytomegalovirus disease)	↓ T cell proliferative response ↑ NK cells, serum Ig, autoantibodies
HEM-1 deficiency [40]	Mutation of HEM-1 causes impaired regulation of actin cytoskeleton, with abnormal lymphocyte development and apoptosis	Recurrent otitis and sinopulmonary infections, splenomegaly, hepatomegaly. Possible development of HLH-like clinical picture	Inverted CD4/CD8 ratio ↑ Senescent T cells, memory T cells Hypergammaglobulinemia
APDS-1 [42,43]	PIK3CD gain of function mutation causes enhanced activation of the mTOR pathway, promoting the proliferation of effector T cells	Splenomegaly, hepatomegaly, recurrent sinopulmonary infections, susceptibility to herpesvirus infections, enteropathy, autoimmunity	↑ Senescent T cells, transitional B cells ↓ Naive T cells Hypogammaglobulinemia/ HIGM
APDS-2 [42,43]	PIK3R1 loss of function mutation causes enhanced activation of the mTOR pathway, promoting the proliferation of effector T cells	Splenomegaly, hepatomegaly, recurrent sinopulmonary infections, susceptibility to herpesvirus infections, enteropathy, autoimmunity, short stature	↑ Senescent T cells, transitional B cells ↓ Naive T cells Hypogammaglobulinemia/ HIGM
APDS-L [42,46]	Loss of function of PTEN causes enhanced activation of the PI3K pathway	Enteropathy, facial dysmorphisms, macrocephaly, neurodevelopmental delay, recurrent respiratory infections. Increased risk of several malignancies	↑ Transitional B cells ↓ Class-switched memory B cells Hypogammaglobulinemia

Abbreviations: AK2 = adenylate kinase 2; APDS = activated phosphoinositide 3-kinase δ syndrome; APDS-L = activated phosphoinositide 3-kinase δ syndrome-like; BENTA = B cell expansion with nuclear factor kappa B (NF-κB) and T cell anergy; CARD11 = caspase recruitment domain family member 11; GLILD = granulomatous lymphocytic interstitial lung disease; HEM-1 = hematopoietic protein 1; HIGM = hyper-IgM syndrome; HL = Hodgkin's lymphoma; IL-7R = interleukin-7 receptor; IL-R2B = interleukin-2 receptor β chain; JAK3 = Janus kinase 3; NHL = non-Hodgkin's lymphoma; NK = natural killer; mTOR = mammalian target of rapamycin; PIK3CD = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit δ; PIK3R1 = phosphoinositide-3-kinase regulatory subunit 1; PTEN = phosphatase and tensin homolog; RAG = recombinase activating genes; STAT = signal transduced and activator of transcription; TRECs = T cell receptor excision circles.

by phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit δ (PIK3CD) GOF mutations (APDS1) and phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1) loss of function (LOF) mutation (APDS2) [41]. The hyperactivation of the PI3K complex, mainly through the

enhanced function of the mechanistic target of rapamycin (mTOR) pathway, leads to a combined immune defect, often associated with reduced naive T cells, elevation of senescent lymphocytes and hypogammaglobulinemia, although the finding of a HIGM is common [42]. Patients with APDS

experience multiple sinopulmonary infections and increased susceptibility to viral infections, in particular caused by herpesviruses. The molecular defect is also responsible for a marked immune dysregulation and lymphoproliferation: lymphadenopathies are evidenced in almost all patients, frequently in association with hepatomegaly and/or splenomegaly, and patients have a higher risk of developing lymphomas (mainly NHL) than the healthy population [43,44]. Moreover, patients show high susceptibility for the development of autoimmunity, mainly autoimmune cytopenias and enteropathy [42, 45]. Lymphadenopathy is one of the leading signs of APDS, frequently being the presentation sign of the disease, and the differential diagnosis with autoimmune lymphoproliferative syndrome (ALPS) or lymphomas is extremely difficult. Pathological examination of lymph nodes often shows disrupted germinal centers, follicular hyperplasia and reduced mantle zones [42]. A similar clinical picture (APDS-like) is observed in patients with loss of function of the phosphatase and tensin homolog (PTEN) gene, implicated in the regulation of the PI3K molecular pathway. In APDS-L lymphoproliferation is less common, and patients are often affected by neurodevelopmental delay and increased risk of different non-lymphoid neoplasms (Table 1) [42,46].

Recognizing APDS is fundamental for the outcome of the disease, as the treatment with immunosuppressive agents, such as sirolimus, specific PI3K inhibitors (leniolisib, nemiralisib) or, in selected patients, hematopoietic stem cell transplantation (HSCT) [42], can improve the clinical course.

Rare PIDs presenting with lymphadenopathy

The finding of a clinically relevant non-infectious lymphadenopathy in patients with defects of the innate immune response such as phagocytic function is rare, being described only in isolated case reports and series of patients with chronic granulomatous disease [47]. Patients with Wiskott–Aldrich syndrome (WAS) rarely develop benign polyclonal lymphoproliferation, as the classical clinical phenotype is featured by immunodeficiency, eczema and thrombocytopenia, but have a higher risk of lymphoid malignancies compared to the general population [48]. Other immunodeficiencies associated with syndromes, including those caused by molecular defects impairing DNA repair [ataxia-teleangiectasia (AT), Nijmegen breakage syndrome (NBS), Bloom syndrome and others] and short telomere syndromes [cartilage-hair hypoplasia (CHH)], are associated with a remarkable risk for the development of lymphoid neoplasms (Table 1). Because, in these syndromes, lymphadenopathy is not part of the classic clinical picture [3,49–52], its finding in patients diagnosed with one of these disorders is highly suggestive of an underlying neoplastic disease.

Among the disorders classified as ‘phenocopies’ of PIDs [4], RAS-associated autoimmune leukoproliferative disease (RALD) is of particular interest, and could present a clinical picture resembling ALPS. RALD, caused by somatic mutations in the RAS signaling pathway (often NRAS or KRAS) is clinically featured by an early onset of a systemic lupus erythematosus (SLE)-like picture, accompanied by hematological involvement (cytopenias), hepatosplenomegaly and lymphadenopathy. In patients with RALD, the development of NHL has been described [53,54].

Immune dysregulation syndromes

In syndromes associated with immune dysregulation, lymphadenopathies can be one of the leading signs of the clinical spectrum (Table 3). Immune dysregulation syndromes are caused by defective lymphocyte apoptosis, accumulation of self-reactive lymphocytes or altered function of regulatory T cells (T_{regs}) (Figure 3). A distinct subclass of immune dysregulation disorders includes diseases associated with increased susceptibility to Epstein–Barr virus (EBV)-induced lymphoproliferation.

Disorders with ineffective apoptosis

ALPS is an inherited disease determined by mutations in genes involved in the first apoptosis signal (FAS) molecular pathway [55], which includes the FAS, FAS ligand (FASL) and caspase-10 (CASP-10) genes, although in approximately 20–30% of patients the molecular diagnosis remains unknown [56]. The defective apoptosis causes the accumulation of circulating and nodal (paracortical) $\alpha\beta$ double-negative T $CD8^+$ cells (abDNT), and self-reactive T cells can also be observed. Patients with ALPS commonly present to clinical attention in the first year of life, with lymphoproliferation being the leading sign of the entire picture. In particular, patients show multiple chronic lymphadenopathies associated with splenomegaly and, frequently, hepatomegaly [56]. Patients can also present with autoimmune cytopenia, more frequently hemolytic anemia and immune thrombocytopenia, while organ-specific autoimmunity is described in a lower percentage of patients [55,56]. Other relevant laboratory findings include altered levels of serum immunoglobulin, more frequently showing polyclonal elevation of IgG; however, hypogammaglobulinemia is also described in a condition partially overlapping with CVID [55]. Reduced soluble FAS ligand levels, impaired apoptotic function, elevated abDNT and high vitamin B12 levels are highly suggestive for the diagnosis [57]. Although histological features are non-specific, in most cases lymph nodes show follicular hyperplasia accompanied by the expansion of small lymphocytes (abDNT)

TABLE 3 Genetic background of immune dysregulation syndromes associated with lymphadenopathies and clinical implications

Disease	Molecular defect	Other clinical features and implications	Main laboratory findings
ALPS-FAS ALPS-sFAS ALPS-FASL ALPS-CASP10 ALPS-U [55,56,57,62]	Mutation of FAS, sFAS, FASL or CAPS-10 finally cause defective lymphocyte apoptosis	Splenomegaly, hepatomegaly, autoimmune cytopenia, other autoimmune diseases (thyroiditis, hepatitis, uveitis)	↑ abDNT cells, serum Ig levels, serum vitamin B12, serum IL-10, IL-18; serum FAS ligand
TET-2 deficiency [60]	TET-2 mutation causes reduced DNA methylation with consequently altered lymphocyte homeostasis, differentiation and apoptosis	Increased susceptibility to infection, splenomegaly, hepatomegaly, autoimmune cytopenia, ALPS-like clinical phenotype	↑ abDNT, serum FAS ligand, serum IL-10 ↓ Th17, Th1, class-switched B cells Hypogammaglobulinemia
IPEX syndrome [64,65]	Mutations of FoxP3 lead to defective maturation of T _{regs}	Autoimmune enteropathy, endocrinopathy, eczematous dermatitis, lymphoproliferation, food allergies, autoimmune disorders (type 1 diabetes, cytopenias, thyroiditis), arthritis	↑ Peripheral eosinophils, serum IgE, CD4 cells
CD25 deficiency [63,71,72]	Mutations of the IL-2R α gene causes reduced activity of the IL-2 receptor, with a consequent deficit in the T cell adaptive response and proliferation of T _{regs}	IPEX-like phenotype. Enteropathy, eczema, splenomegaly, hepatomegaly Susceptibility to viral and bacterial infections	↓ T cell proliferative response, CD4/CD8 ratio
CTLA-4 deficiency [63,66,67,70]	Mutation of CTLA-4 causes reduced T _{regs} suppressive activity, with ineffective inhibition of co-stimulatory molecules CD80/CD86 on APCs	IPEX-like phenotype. Enteropathy, splenomegaly, respiratory infections, autoimmunity (cytopenia, thyroiditis, arthritis, uveitis), psoriasis, GLILD	↓ Peripheral lymphocytes, naive T cells, T _{regs} CD19 cells, switched-memory B cells, NK cells Hypogammaglobulinemia Potentially normal laboratory findings
LATAI [63,68,69,70]	LRBA mutation causes reduced CTLA-4 expression on T _{regs} surface, with consequent altered T _{regs} suppressive activity	IPEX-like or ALPS-like phenotype Splenomegaly, hepatomegaly. Enteropathy, autoimmunity (cytopenia, hepatitis, uveitis, diabetes), respiratory infections, bronchiectasis. GLILD	↓ Peripheral lymphocytes, T _{regs} , memory B cells Hypogammaglobulinemia Potentially normal laboratory findings
BRIDA [63,73]	BACH-2 mutation causes impaired germ center reactions (B cell maturation, class-switching) and T cell differentiation, with T _{regs} deficiency	CVID-like phenotype, enteropathy, sinopulmonary infections, splenomegaly	↑ Th1 cells, transitional B cells ↓ Tregs, T cell proliferation, memory B cells, class-switched B cells Hypogammaglobulinemia
STAT1 GOF [63,74,78,79]	The mutation causes defective production of Th17 cells	IPEX-like phenotype, predisposition to mucocutaneous candidiasis and autoimmunity (thyroiditis)	↓ Th17 cells
STAT3 GOF [63,74,77]	The mutation causes impaired T _{reg} proliferation (via indirect inhibition of STAT5), reduced CD25 expression. Probably altered Th17 proliferation and function	IPEX-like phenotype. Enteropathy, eczema, severe infections, growth retardation, and multiorgan autoimmunity (i.e. diabetes, thyroiditis, arthritis), GLILD	↓ Memory B cells, T _{regs} , double-negative T cells Hypogammaglobulinemia Potentially normal laboratory findings

(Continues)

TABLE 3 (Continued)

Disease	Molecular defect	Other clinical features and implications	Main laboratory findings
SOCS-1 deficiency [80]	SOCS1 mutations cause an uncontrolled activation of STAT-dependent pathways, enhanced T cell proliferation and reduced T _{reg} integrity and function	Early-onset autoimmunity (cytopenia, SLE-like phenotype, arthritis, thyroiditis), hepatomegaly, splenomegaly	↓ T _{regs} , switched-memory B cells Anti-nucleous antibodies, other autoantibodies (anti-dsDNA, anti-phospholipid)
PKCD [61]	PKCD mutations cause defective lymphocyte apoptosis, enhanced IL-2 production and T cell proliferation, enhanced BCR signaling. Altered immune tolerance	Hepatomegaly, splenomegaly, SLE-like phenotype (articular, hematological, cutaneous, and renal involvement), antiphospholipid syndrome	Hypogammaglobulinemia Anti-nucleous antibodies, other autoantibodies (anti-dsDNA, anti-phospholipid)

Abbreviations: abDNT = $\alpha\beta$ double-negative T cells; ALPS = autoimmune lymphoproliferative syndrome; APCs = antigen-presenting cells; BACH-2 = BTB domain and CNC homolog 2; BCR = B cell receptor; BRIDA = BACH2-related immunodeficiency and autoimmunity; CASP10 = caspase 10; CTLA-4 = cytotoxic T lymphocyte antigen-4; FAS = first apoptosis signal, FASL = FAS ligand; FoxP3 = forkhead box protein 3; GLILD = granulomatous lymphocytic interstitial lung disease; GOF = gain-of-function; HL = Hodgkin's lymphoma; IGF-1 = insulin growth factor 1; IL-R2A = -interleukin-2 receptor α chain; IPEX = immune dysregulation, polyendocrinopathy, enteropathy, X-linked; LATAI = LRBA deficiency with autoantibodies, T_{reg} cell defects, autoimmune infiltration and enteropathy; LRBA = lipopolysaccharide (LPS)-responsive and beige-like anchor; NHL = non-Hodgkin's lymphoma; PKCD = protein kinase C δ deficiency; sFAS = somatic mutation of FAS; SLE = systemic lupus erythematosus; SOCS1 = suppressor of cytokine signaling 1; STAT = signal transduced and activator of transcription; T_{regs} = regulatory T cells, TET-2 = 10–11 translocation methylcytosine dioxygenase 2.

with high proliferative rate and plasma cells in the paracortical area [55,58]. A correct diagnosis of ALPS is fundamental to provide a strict follow-up for the patients, as the disease is associated with a high risk of developing lymphomas, predominantly Hodgkin's lymphoma (HL) [59]. Interestingly, an ALPS-like clinical picture with susceptibility to HL and NHL and impairment of the FAS-dependent apoptotic pathway can be observed in other monogenic disorders, such as 10–11 translocation methylcytosine dioxygenase 2 (TET2) deficiency [60] (Table 3).

Another disease caused by impaired apoptosis is protein kinase C δ deficiency (PKCD). PKCD is featured by defective apoptosis of B and T cells, increased lymphocyte proliferation and impaired immune tolerance. The disease presents with a clinical feature at a crossroad between PIDS and immune dysregulation syndromes, with lymphoproliferation triggered by viral infections being the leading signs of the disease. Moreover, patients can produce different specificities of autoantibodies, resulting in a systemic lupus erythematosus (SLE)-like phenotype [61]. Both ALPS and PKCD are commonly treated with immunosuppressive agents, with HSCT being reserved for refractory cases of ALPS [62].

Disorders of regulatory T cells

The immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, caused by mutations leading to a loss of function of forkhead box protein 3 (FoxP3), is the main condition in the group of T_{regs}-associated disorders (Tregopathies) [63]. IPEX is featured by the classical

clinical triad of autoimmune enteropathy, endocrinopathy and early-onset severe eczematous dermatitis [64]. Given the central role of FoxP3 in both the development and function of T_{regs}, the consequence carried by the molecular defect is an immune dysregulation [63], which can be accompanied by lymphoproliferation. Other classical signs and symptoms include the presence of peripheral eosinophilia, food allergies and autoimmune disorders, particularly type I diabetes and autoimmune cytopenias [64]. Patients with IPEX show lymphadenopathies in approximately 15% of cases [65], while lymphomas have been described only in isolated cases [64].

In other conditions featuring impaired function of T_{regs}, but showing wild-type FoxP3, patients can present with an IPEX-like clinical phenotype, whose differences in the prevalence of the single disease manifestations depend upon the specific molecular defect [65]. In particular, the group of Tregopathies includes cytotoxic T lymphocyte antigen-4 (CTLA-4) deficiency, lipopolysaccharide (LPS)-responsive and beige-like anchor (LRBA) deficiency with autoantibodies, T_{reg} cell defects, autoimmune infiltration and enteropathy (LATAI), BTB domain and CNC homolog 2 (BACH-2) haploinsufficiency, CD25 deficiency and signal transducer and activator of transcription (STAT)-related disorders (Table 3) [63].

The molecular pathogenesis of the T_{reg} alterations in CTLA-4 deficiency and LATAI is strictly connected. In particular, CTLA-4, expressed by T_{regs}, is pivotal in causing the reduction of the expression of the co-stimulatory molecules CD80 and CD86 on the antigen-presenting cell (APC) surface [66], and LRBA inhibits the lysosomal degradation of CTLA-4 (Figure 3). Therefore, the clinical phenotypes of the

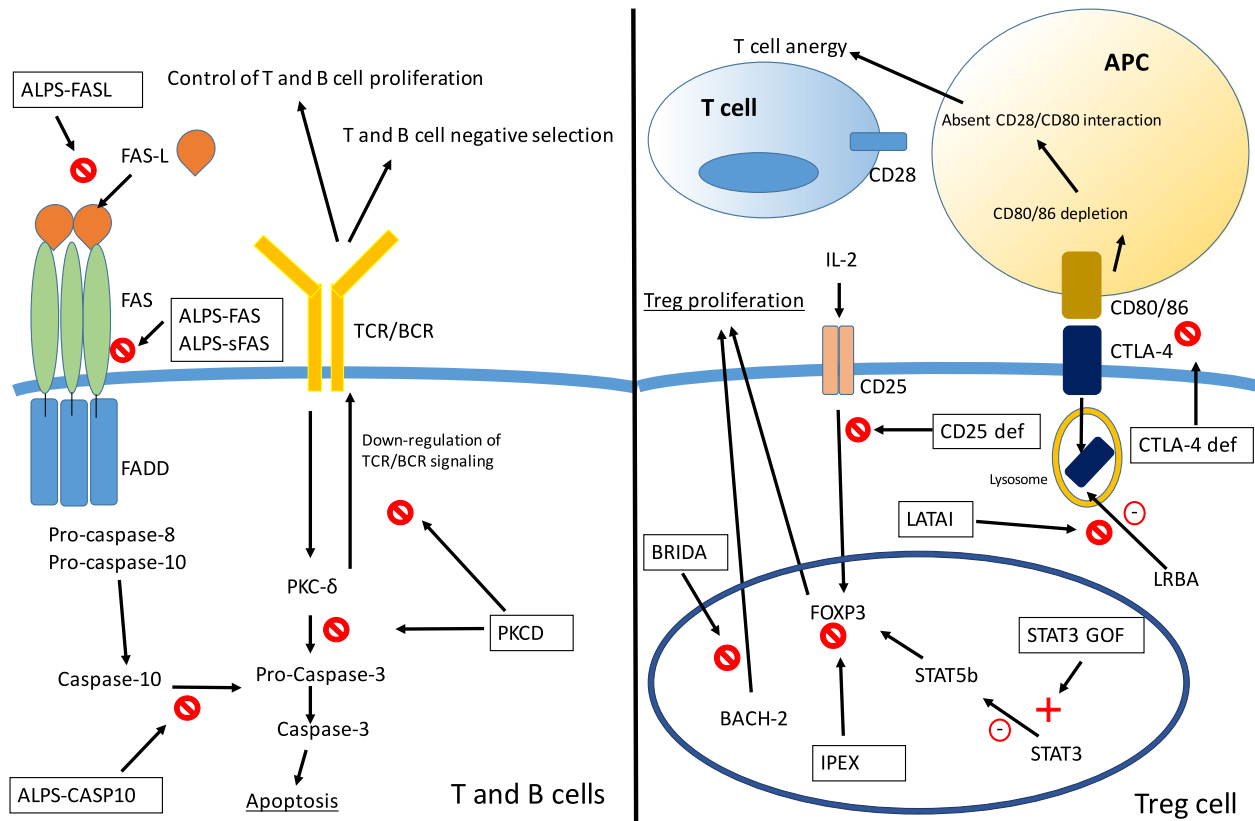


FIGURE 3 Summary of the molecular mechanisms leading to immune dysregulation syndromes. (a) The molecular mechanisms associated with the development of immune dysregulation in disorders with ineffective apoptosis. When the first apoptosis signal (FAS) binds FAS ligand (FASL), the apoptotic pathway is initiated, as FAS-associated protein with death domain (FADD) promotes the activation of pro-caspase 8 and pro-caspase 10, responsible for the initiation of apoptosis. In autoimmune lymphoproliferative syndrome-FAS (ALPS-FAS), ALPSFASL) and ALPS-caspase 10 (CASPI0) the molecular defect is responsible for an impairment of the first molecular steps of the apoptotic cascade. Protein kinase C δ (PKC- δ) promotes the apoptosis through a caspase-3 dependent mechanism, and acts by down-regulating the B cell receptor (BCR) and T cell receptor (TCR) signaling, thus reducing the lymphocyte proliferation. Therefore, in PKC- δ deficiency (PKCD) the apoptotic defect is accompanied by enhanced lymphocyte proliferation. (b) Mechanisms responsible for immune dysregulation and lymphadenopathy in diseases affecting regulatory T cells (T_{regs}) functioning. Forkhead box protein 3 (FoxP3), which is deficient in immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), is central for T_{regs} proliferation and activity. CD25 is important in activating interleukin (IL)-2-dependent signaling, and therefore in promoting the transcription of FoxP3, which is impaired in CD25 deficiency. Signal transducer and activator of transcription (STAT)-5b is an activator of FoxP3, which is inhibited by STAT-3. In STAT-3 gain-of-function (GOF), the enhanced inhibition of STAT-5 finally leads to reduced FoxP3 activity and T_{regs} proliferation. Also, the BTB domain and CNC homolog 2 (BACH-2) has a role in promoting T_{reg} proliferation, which is altered in patients with BACH2-related immunodeficiency and autoimmunity (BRIDA). Cytotoxic T lymphocyte antigen 4 (CTLA-4), through interaction with the co-stimulatory molecules CD80/CD86 on the antigen-presenting cells (APC) surface, reducing their availability for the interaction with CD28 expressed by T cells. CTLA-4 deficiency results in ineffective inhibition of co-stimulatory signaling, leading to enhanced activation of T cells. Finally, lipopolysaccharide-responsive and beige-like anchor (LRBA) inhibits the lysosomal degradation of CTLA-4, and in LRBA deficiency with autoantibodies, T_{reg} cell defects, autoimmune infiltration and enteropathy (LATAI) a secondary CTLA-4 deficiency is observed

diseases share many common features. They are both associated with hypogammaglobulinemia, increased risk of infections (with a higher frequency of life-threatening infections in LATAI) and autoimmune manifestations, including autoimmune cytopenia and enteropathy. Additionally, up to 50% of the patients with CTLA-4 mutations show lymphadenopathy [67], which is observed in a similar percentage of patients with LATAI [65,68]. Therefore, both diseases could present a clinical picture that can resemble both IPEX and ALPS. In CTLA-4 and LATAI, patients show an increased risk of HL

and NHL [67–69]. Interestingly, a recent systematic review evidenced that malignant lymphoproliferation is more common in patients with CTLA-4 deficiency [70] (Table 1).

Immune dysregulation and lymphoproliferation are part of the clinical spectrum observed in patients with CD25 deficiency, which have ineffective IL-2 signaling with consequently reduced activation of T cells and reduced proliferation of T_{regs} [71,72], and in those affected by the BACH2-related immunodeficiency and autoimmunity (BRIDA), a rare condition featured by impaired reactions of the germ center and

enhanced proliferation of Th1 cells with a reduced number of circulating T_{regs} [73].

A clinical picture of immune dysregulation is also observed in patients with molecular defects involving the STAT genes, which are implicated in the signaling pathways activated by different cytokines through JAK-mediated phosphorylation. In particular, GOF mutations of STAT-1 and STAT-3 can show features of immunodeficiency, autoimmunity and lymphoproliferation [74]. Both STAT-1 and STAT-3 are activated by IL-2, while IL-6 participates only in the induction of STAT-3 phosphorylation [74].

In STAT-3 GOF, reduced proliferation of T_{regs}, decreased expression of CD25 and altered T helper type 17 (Th17) cell proliferation are observed [74]. Clinically, patients present lymphadenopathy and experience severe infections, growth retardation and multi-organ autoimmunity (i.e. diabetes, thyroiditis arthritis) [75–77]. Moreover, an increased risk of HL and NHL has been described [63]. Patients with STAT-1 GOF show reduced Th17 proliferation, resulting in increased susceptibility to different infections, mainly mucocutaneous candidiasis [74]. The disease is also associated with immune dysregulation and autoimmunity [78]. The molecular mechanisms leading to immune dysregulation and T_{reg} impairment have not been completely elucidated. Although lymphadenopathy is not part of the classical clinical picture of STAT-1 GOF, it has been recently described in two patients in whom HL was also documented [79]. Notably, as suppressor of cytokine signaling 1 (SOCS1) is implicated in the down-regulation of the JAK/STAT pathway, its haploinsufficiency is associated with lymphocyte hyperactivity, autoimmunity and lymphoproliferation [80].

Although there is a significant clinical overlap between the different Tregopathies and their definitive treatment is represented by HSCT, reaching a molecular diagnosis can help in providing specific targeted treatments, such as the CTLA-4 analogue abatacept in CTLA-4 deficiency and LRBA deficiency, JAK inhibitors (baricitinib, ruxolitinib) in STAT-related disorders and tocilizumab in STAT-3 GOF [81,82].

Diseases with EBV-related lymphoproliferation

EBV infection, if not adequately controlled by the immune system, can result in polyclonal B cell activation and proliferation and potentially in the development of lymphoma, as the infectious agent is able to interfere with cellular apoptosis and express proteins that induce B cell activation [83].

An exuberant EBV-associated lymphoproliferation is described in different PIDs, in most cases depending on defects of the cellular immune response. In particular, it is reported in patients with defects in T cell proliferative response to mitogens, in defective early T cell receptor (TCR) signaling or

co-stimulatory molecules (Table 4) [84–93]. All the diseases mentioned cause persistent or recurrent lymphadenopathies triggered by an uncontrolled EBV infection and prolonged EBV viremia, and are associated with an increased risk of developing EBV-associated lymphoid malignancies. Although most of these conditions are caused by molecular defects selectively impairing the immune response against EBV, in disorders depending upon a non-selective immune defect patients can experience also severe infections caused by other pathogens [84]. Indeed, disorders of T cell proliferative response and signaling, including RAS guanyl-releasing protein 1 (RASGRP1), CTP synthase 1 (CTPS1) and interleukin-2-inducible T cell kinase (ITK) deficiencies, are associated with an increased risk of other severe viral infections [caused by cytomegalovirus, herpes simplex virus, varicella-zoster virus, human papillomavirus (HPV) and others], bacterial and fungal infections and virus-associated neoplasms (i.e. HPV-related) [84,86]. Two other peculiar conditions featured by non-EBV selective immune impairment are represented by X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia (XMEN) disease and serine/threonine kinase 4 (STK4) deficiency. XMEN is a rare PID caused by a deficiency of the magnesium transporter 1 (MAGT1) gene. It presents in males with recurrent sinopulmonary infections, otitis and chronic lymphadenopathy, often accompanied by splenomegaly. In the disease, sharing common clinical features with ALPS, the lymphoproliferation can be both EBV-related and EBV-independent and carries also a significant risk of developing lymphoid neoplasms [85,94]. In STK4 deficiency, a PID featured by lymphopenia mainly affecting T CD4 cells, patients experience recurrent infections with increased susceptibility to EBV and potential development of both benign lymphoproliferation and lymphoma. The role of STK4 in the surveillance against the development of neoplasms underlies the elevated risk of lymphomas and leukemia in these patients [88]. The clinical relevance of EBV-related disorders points out the importance of performing a PCR analysis for EBV DNA in patients with features of immunodeficiency or immune dysregulation and lymphoproliferation, as well as the necessity of an EBV encoding region (EBER) *in-situ* hybridization on the histological samples from these patients [95]. Finally, patients with defective killing function, as reported in X-linked proliferative syndrome 1 (XLP1) and XLP2 or patients with disorders involving check-points of the cellular cycle, have enhanced susceptibility to the development of EBV-associated hemophagocytic lymphohistiocytosis (HLH) (Table 4) [96–98]. Among these, XLP1 is of particular interest, as its complex clinical picture is not limited to EBV-related HLH (in which the presence of lymphadenopathy is not the prominent feature), but includes hypogammaglobulinemia with immune dysregulation, EBV-related lymphoproliferation and increased susceptibility to

TABLE 4 Disorders associated with increased susceptibility to EBV-related lymphadenopathy

Disease	Molecular defect	Other clinical/laboratory features and implications
RASGRP1 deficiency [84,86]	Defective T cell proliferative response to mitogens, reduced expression of CTPS1	Susceptibility to CMV, HPV, HSV, bacterial and fungal infections
CTPS1 deficiency [84,89]	Defective T cell proliferation after activation of TCR. No deficit in effector function	Recurrent bacterial and viral infections
ITK deficiency [84,90]	Defective TCR signaling, with impaired expansion and effector function of CD8 cells	Increased risk of virus-associated neoplasia [i.e. HPV associated]
XMEN [84,85,94]	MAGT1 deficiency causes impaired TCR signaling and defective NK2GD expression on CD8 and NK cells, responsible for a defective killing of EBV-infected cells	Recurrent sinopulmonary infections, otitis, splenomegaly. ↑Peripheral B cells, inverted CD4/CD8 ratio
CD70 deficiency [84,91,93]	Defective CD70/CD27 interaction, important in T cell survival and effector function, including the expansion against EBV	Highly selective for EBV infections Hypogammaglobulinemia
CD27 deficiency [84,92,93]	Defective CD70/CD27 interaction, important in T cell survival and effector function, including the expansion against EBV	Highly selective for EBV infections Potential EBV-associated HLH
CD137 deficiency [84,87]	TNFRSF9 mutations cause Impaired expansion of EBV-specific T cells, for the absence of co-stimulatory activity mediated by CD137	Highly selective for EBV infections. Chronic EBV viremia. Potential EBV-associated HLH
STK4 deficiency [88]	STK4 mutations lead to enhanced T cell apoptosis and reduced T cell proliferation. STK4 is also a regulator of cellular checkpoints	Recurrent infections. Reduced levels of T cells. Hepatomegaly, splenomegaly
XLP1 [84,99,100]	Mutations in the SH2DIA gene, causing a defective killing of EBV-infected cells by T and NK cells	EBV-associated HLH. Hypogammaglobulinemia
XLP2 [84,96]	XIAP mutations, causing enhanced T cell apoptosis and inflammasome dysregulation	EBV or CMV-associated HLH. Other inflammatory disorders [IBD]
FAAP24 deficiency [97]	FAAP24 mutation causes altered DNA repair and ineffective checkpoint response	EBV-associated HLH

Abbreviations: CTPS1 = CTP synthase 1; EBV = Epstein–Barr virus; FAAP24 = Fanconi anemia-associated protein 24; HL = Hodgkin's lymphoma; HLH = hemophagocytic lymphohistiocytosis; ITK = interleukin-2-inducible T cell kinase; MAGT1 = magnesium transporter 1; NHL = non-Hodgkin's lymphoma; NK = natural killer; NK2GD = natural killer group 2 member; DRASGRP1 = RAS guanyl-releasing protein 1; SH2DIA = SH2 domain-containing protein 1A; STAT = signal transduced and activator of transcription; STK4 = serine/threonine kinase 4; TNFRSF9 = tumor necrosis factor receptor subfamily 9; XIAP = X-linked inhibitor of apoptosis; XMEN = X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia. XLP = X-linked proliferative syndrome.

the development of lymphoid malignancies, particularly NHL [99,100] (Table 1).

Autoinflammatory disorders

Autoinflammatory disorders are a wide spectrum of diseases featured by an uncontrolled inflammatory response, caused by defects in the structure and function of the inflammasome. Their most recognized clinical presentation is represented by recurrent episodes of fever accompanied by other signs or symptoms, which may include lymphadenopathy [101]. Differently from the other diseases discussed in this review, autoinflammatory disorders are not associated with the development of lymphoid malignancies, but the clinical phenotype is often difficult to interpret. Lymphadenopathy represents a prominent clinical feature of the periodic fever, aphthous

stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome and hyper-IgD syndrome (HIDS), although it is rarely also described in patients with other autoinflammatory disorders (Table 5) [102–107].

PFAPA syndrome is the most common autoinflammatory disorder of childhood [101], with a mean age at onset of 2–4 years, and presents with recurrent episodes of fever with a duration of 3–6 days, accompanied by cervical lymphadenopathy, pharyngitis and aphthosis [106]. Laboratory examinations are non-specific, but typically show elevation of inflammatory markers during the febrile episodes, with normalization in the intercritical period [106]. Given this clinical phenotype, patients are usually referred to immunologists, infectious disease specialists or otolaryngologists [108]. However, in a subgroup of patients recurrent fever and lymphadenopathy can be the leading signs of the disease, thus justifying the request of a hematological consultation. The absence of an

TABLE 5 Genetic background of autoinflammatory disorders associated with lymphadenopathies and clinical implications

Disease	Molecular defect	Other clinical features and implications	Laboratory findings
PFAPA syndrome [106, 108]	Unknown	Periodic episodes of fever (duration 3–5 days, recurrence 21–28 days). Pharyngitis, aphthosis, possible abdominal pain	↑ Inflammatory biomarkers during the febrile episodes
HIDS [107, 109]	Mutation of MVK causes accumulation of mevalonic acid and reduced production of isoprenoids	Periodic fever (duration 3–8 days, recurrence every 2–8 weeks), abdominal pain arthralgia/arthritis, cutaneous rash, splenomegaly, hepatomegaly, vomiting, serositis, aphthosis	↑ Inflammatory biomarkers during the febrile episodes, serum cytokines, serum IgD ↓ MVK activity
FMF [103]	Mutation of MEFV causes the production of dysfunctional protein pyrin, with consequent activation of the inflammasome resulting in an enhanced inflammatory response	Periodic fever (duration 1–3 days, variable recurrence), abdominal pain arthralgia/arthritis, cutaneous rash, arthralgia/arthritis, serositis	↑ Inflammatory biomarkers during the febrile episodes, serum cytokines
TRAPS [102]	Mutations of TNFRSF1A cause reduced serum TNFR (with enhanced TNF-induced response), defective autophagy, and increased damage by reactive oxygen species	Periodic fever (duration 7–21 days, 2–4 episodes/year), cutaneous rash, abdominal pain conjunctivitis, ocular pain, myalgia, arthralgia/arthritis	↑ Inflammatory biomarkers during the febrile episodes, serum cytokines. ↓ Serum TNFR
Blau syndrome [104]	NOD2 mutation, causing activation of NF-κB	Granulomatous arthritis, uveitis, dermatitis. Less common: sialoadenitis, vasculitis, erythema nodosum, neuropathies, nephritis, hepatic and splenic granulomas, interstitial lung disease	↑ Inflammatory biomarkers (chronic elevation)
DADA-2 [105]	CECR1 mutation causes deficient activity of ADA-2, resulting in imbalanced monocyte differentiation, increased activity of neutrophils	Vasculitis (polyarteritis nodosa), cutaneous rash, livedo reticularis, musculoskeletal and renal involvement, susceptibility to stroke Immune dysregulation, splenomegaly, hepatomegaly. Increased risk of sinopulmonary infections and herpesvirus infections	↑ Inflammatory biomarkers ↓ Memory B cells, terminally differentiated B cells; plasma cells Hypogammaglobulinemia (↓IgM)
Disease	Molecular defect	Other clinical features and implications	Laboratory findings
PFAPA syndrome [106, 108]	Unknown	Periodic episodes of fever (duration 3–5 days, recurrence 21–28 days). Pharyngitis, aphthosis, possible abdominal pain	↑ Inflammatory biomarkers during the febrile episodes
HIDS [107, 109]	Mutation of MVK causes accumulation of mevalonic acid and reduced production of isoprenoids	Periodic fever (duration 3–8 days, recurrence every 2–8 weeks), abdominal pain arthralgia/arthritis, cutaneous rash, splenomegaly, hepatomegaly, vomiting, serositis, aphthosis	↑ Inflammatory biomarkers during the febrile episodes, serum cytokines, serum IgD ↓ MVK activity

Abbreviations: ADA-2 = adenosine deaminase-2; CECR1 = cat eye syndrome chromosome region 1; DADA-2 = adenosine deaminase-2 deficiency; FMF = familial Mediterranean fever; HIDS = hyper-immunoglobulin (Ig)D syndrome; MEFV = Mediterranean fever; MVK = mevalonate kinase; NF-κB = nuclear factor kappa B; NOD2 = nucleotide-binding oligomerization domain 2; PFAPA = periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis; TNFR = tumour necrosis factor receptor; TNFRSF1A = tumour necrosis factor receptor superfamily member 1A; TRAPS = tumour necrosis factor receptor-associated periodic syndrome.

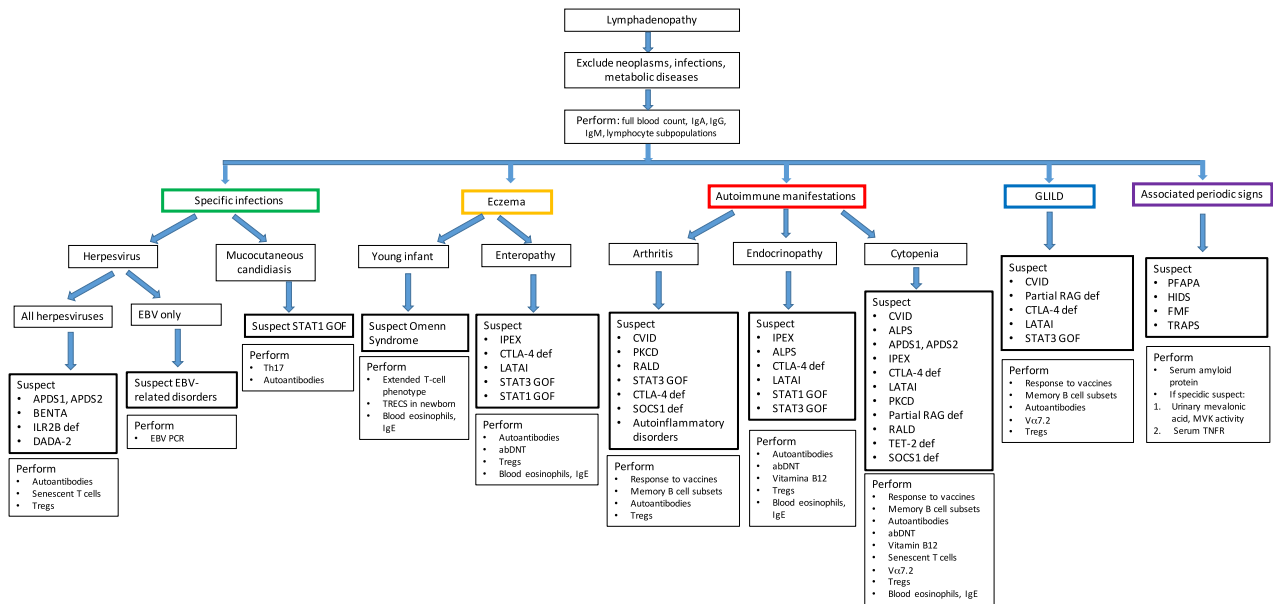


FIGURE 4 Diagnostic approach to lymphadenopathies in patients with immune disorders. The figure shows an approach to the diagnosis of immune diseases (immunodeficiencies, immune dysregulation and autoinflammatory disorders) associated with lymphoproliferation. The approach is based on the identification of specific clinical signs, including features of autoimmunity (arthritis, cytopenia, endocrinopathy), the finding of eczema, specific infectious patterns, periodic disease course and respiratory involvement, in the form of granulomatous lymphocytic interstitial lung disease (GLILD)

identified causative mutation contributes to complicating the diagnostic approach to the disease.

HIDS, caused by mutations of the mevalonate kinase (MVK) gene, usually shows onset during the first year of life, and most of the patients present to clinical attention before the fifth year of life. Patients with HIDS experience recurrent episodes of fever occurring every 2–8 weeks with a duration of 3–7 days, associated with a wide spectrum of symptoms such as abdominal pain, cutaneous rash, arthralgia or arthritis [109]. In most patients, during the febrile episodes lymphadenopathy is present, mainly in the cervical region, and can be accompanied by splenomegaly and hepatomegaly [107]. Differently from PFAPA syndrome, which usually resolves in scholar age, a significant percentage of patients with HIDS continue to experience febrile episodes and the associated signs and symptoms after adolescent age [109]. During the episodes, an elevation of inflammatory markers, including serum amyloid protein, is observed, while the levels of serum cytokines (IL-1 β , IL-6) also remain elevated in many cases in the intercritic phase. Elevated levels of IgD are highly suggestive for HIDS but can be absent in some patients, thus not representing a sensible biomarker [107].

CONCLUSIONS AND DIAGNOSTIC IMPLICATIONS

During past decades, following the rapid advances in the knowledge of the molecular and immunological mechanisms

underlying the pathogenesis of the immune diseases, new clinical entities at the crossroad of immunodeficiency, immune dysregulation and autoinflammation have been disclosed and some well-known diseases have been reclassified. This makes the diagnostic process of these conditions a great challenge, due to the need to dissect the prevalent pathogenic aspects among the above-mentioned diseases. In this work, we provide an overview of the most relevant PIDs associated with lymphadenopathy, including diseases with immune dysregulation and autoinflammatory disorders, summarizing their pathogenic aspects and clinical features. Beyond the genetic analysis, an extensive approach focused upon the recognition of the clinical signs and immunological features of the single condition (after a wide critical reasoning to exclude infectious, oncological and hematological diseases) can significantly help in the formulation of the diagnosis. Together with the known classic red flags for PIDs (high susceptibility to infections, mainly towards opportunistic pathogens or restricted to the same ones, the evidence of autoimmunity or other signs of immune dysregulation), some peculiar manifestations such as severe eczema, a periodic disease course or the finding of GLILD on computerized tomography (CT) scan are relevant warning signs, helping in the diagnostic process. Therefore, with the purpose of guiding the clinician towards a diagnostic assessment, we elaborated an algorithm focusing upon the main clinical signs at presentation (Figure 4). Although most of the described conditions are associated with an increased risk of infections, a peculiar infectious pattern can help in driving the diagnostic

process. Indeed, the presence of severe herpesvirus infection is common in disorders featured by a combined immune defect (i.e. APDS), while mucocutaneous candidiasis suggests the diagnosis of STAT-1 GOF, thus highlighting the importance of performing complete microbiological investigations (serological tastings, blood cultures, PCR for viral genomes and analysis of histological samples) in these patients. The finding of eczema and enteropathy in association with lymphadenopathy is strongly suggestive of the diagnosis of IPEX or other Tregopathies (CTLA-4 deficiency, LATAI), while the simultaneous presence of eczema and diffuse lymphoproliferation in the newborn can lead to the suspect diagnostic of OS, particularly when it is associated with peripheral eosinophilia [110]. Also, the identification of autoimmunity can provide important indications for the diagnostic process. Indeed, CVID, ALPS and APDS frequently present with autoimmune cytopenias, while arthritis is more commonly evidenced in patients with PKCD and RALD (also in the context of an SLE-like clinical phenotype), and autoimmune endocrinopathies are one of the hallmarks of IPEX syndrome and related disorders. A periodical clinical course featured by the recurrence of lymphadenopathies, fever and other symptoms (pharyngitis, serositis and others) should represent a warning sign for the diagnosis of an autoinflammatory disorder. Finally, in patients with respiratory involvement, the evidence of GLILD supports the diagnostic suspect of CVID, CTLA-4 deficiency, LATAI or STAT-3 GOF.

Despite the significant overlap evidenced in the clinical and immunological pictures of immunodeficiencies and immune dysregulation syndromes associated with lymphoproliferation, an adequate clinical assessment could guide the diagnostic approach and execution of the appropriate genetic investigations. Further research will help in more clearly defining the clinical and immunological features associated with different PIDs, leading to the formulation of genotype–phenotype correlations and giving a basis to provide disease-specific follow-up and therapeutic indications. In conclusion, due to the rarity and multi-faceted complexity of these conditions, deep critical reasoning of the clinician first observing the patient and the close collaboration with a multi-disciplinary group experienced in immunodeficiency and autoinflammation are necessary to provide an adequate diagnostic approach.

ACKNOWLEDGEMENTS

Not applicable.

CONFLICT OF INTERESTS

The authors declare that they have no financial disclosures or conflicts of interest.

AUTHOR CONTRIBUTIONS

Giorgio Costagliola wrote the manuscript, which was critically revised by Rita Costagliola. Both authors contributed

to manuscript revisions and read and approved the submitted version.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: 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>