

The Etiologic Landscape of Lymphoproliferation in Childhood: Proposal for a Diagnostic Approach Exploring from Infections to Inborn Errors of Immunity and Metabolic Diseases

Giorgio Costagliola¹, Emanuela De Marco¹, Francesco Massei¹, Giulia Roberti², Fabrizio Catena¹, Gabriella Casazza¹, Rita Consolini³

¹Section of Pediatric Hematology and Oncology, Azienda Ospedaliero-Universitaria Pisana, Pisa, 56126, Italy; ²Pediatrics Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, 56126, Italy; ³Section of Clinical and Laboratory Immunology, Pediatric Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, 56126, Italy

Correspondence: Giorgio Costagliola, Section of Pediatric Hematology and Oncology, Azienda Ospedaliero-Universitaria Pisana, Pisa, 56126, Italy, Tel +39-050992841, Email giorgio.costagliola@hotmail.com; giorgio.costagliola@ao-pisa.toscana.it,

Abstract: Lymphoproliferation is defined by lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytic organ and tissue infiltration. The most common etiologies of lymphoproliferation are represented by infectious diseases and lymphoid malignancies. However, it is increasingly recognized that lymphoproliferative features can be the presenting sign of rare conditions, including inborn errors of immunity (IEI) and inborn errors of metabolism (IEM). Among IEI, lymphoproliferation is frequently observed in autoimmune lymphoproliferative syndrome (ALPS) and related disorders, common variable immunodeficiency (CVID), activated phosphoinositide 3-kinase δ syndrome, and Epstein-Barr virus (EBV)-related disorders. Gaucher disease and Niemann-Pick disease are the most common IEMs that can present with isolated lymphoproliferative features. Notably, other rare conditions, such as sarcoidosis, Castleman disease, systemic autoimmune diseases, and autoinflammatory disorders, should be considered in the differential diagnosis of patients with persistent lymphoproliferation when infectious and malignant diseases have been reasonably ruled out. The clinical features of lymphoproliferative diseases, as well as the associated clinical findings and data deriving from imaging and first-level laboratory investigations, could significantly help in providing the correct diagnostic suspicion for the underlying etiology. This paper reviews the most relevant diseases associated with lymphoproliferation, including infectious diseases, hematological malignancies, IEI, and IEM. Moreover, some practical indications to orient the initial diagnostic process are provided, and two diagnostic algorithms are proposed for the first-level assessment and the approach to persistent lymphoproliferation, respectively.

Keywords: lymphadenopathy, splenomegaly, Hodgkin lymphoma, common variable immunodeficiency, autoimmune lymphoproliferative syndrome, gaucher disease

Introduction

Lymphoproliferation is a pathologic condition defined by the presence of lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytic organ and tissue infiltration. These manifestations represent common features observed in patients with infectious diseases, that can be clinically expressed with diffuse lymphoproliferation (especially in case of viral infections) or localized involvement, as observed in patients with lymphadenitis.¹ Lymphoproliferative features are also a hallmark of hematological malignancies, including those with prominent lymph nodal localizations (lymphomas) and those with primary bone marrow involvement and secondary lymph nodal spreading (leukemias). Apart from the infectious and malignant etiologies, the role of lymphoproliferative features as presenting signs of inborn errors of immunity (IEI) and inborn errors of metabolism (IEM) is being increasingly investigated.²⁻⁴ Moreover, systemic autoimmune diseases, autoinflammatory disorders, and rare conditions such as sarcoidosis and Castleman diseases can also present with isolated lymphoproliferation.

There are also some significant overlaps in the lymphoproliferative manifestations of IEI, infectious diseases, and hematological malignancies, that further complicate the etiologic and diagnostic scenario. Indeed, while transient lymphoproliferation usually occurs in childhood without consequences, long-standing or recurrent lymphoproliferation is associated with an increased risk of malignant transformation. This is particularly notable in the case of patients suffering from IEI who have an increased susceptibility to Epstein-Barr virus (EBV) infection and a consequent high risk of development of clonal, malignant lymphoproliferation.^{2,3}

Therefore, the clinical approach to patients presenting with lymphoproliferative features is of great complexity, and the diagnosis of some conditions is often delayed in clinical practice.

In this paper, the most relevant clinical characteristics of lymphoproliferation in the context of infectious diseases, hematological malignancies, IEI, and IEM are reviewed. Furthermore, some practical suggestions to orient the diagnostic process are provided and elaborated in the proposal of two diagnostic algorithms, which are respectively directed to the identification of infections and malignancies in the first-level diagnostic assessment and to the search for rarer conditions in the approach to persistent lymphoproliferation.

What is Known: Lymphoproliferation in Infectious Diseases and Hematological Malignancies

Infections and malignancies are the most well-known causes of lymphoproliferation,⁵ and the initial diagnostic approach is commonly directed to the identification of these conditions. Specific clinical and epidemiological features, together with the results of first-level laboratory investigations and imaging are, in most of cases, able to discriminate between these two entities.

Infectious Diseases

Viral infections can be responsible for the development of a clinical picture of lymphoproliferation with variable extension, ranging from localized lymphadenopathies to diffuse forms associated with splenomegaly and hepatomegaly. Among the pathogens, EBV and cytomegalovirus (CMV) are the most frequently involved in determining lymphoproliferative phenotypes, often in association with systemic involvement (fever, malaise), pharyngitis, and hepatic inflammation. In these conditions, also transient cytopenia (thrombocytopenia, neutropenia) can be observed.^{5,6} Differently, the agents commonly implicated in upper respiratory infections (including adenovirus, influenza, and parainfluenza virus) are associated with acute localized reactive lymphadenitis.¹

A peculiar case is represented by HIV. In this condition, lymphoproliferation is often reactive to the infection and presents with multiple or localized lymphadenopathies, which are initially featured by follicular hyperplasia with subsequent germ center involution.⁷ In patients with lower CD4+ counts, persistent HIV-related lymphadenopathy can be observed, more frequently involving the neck;⁷ furthermore, in HIV patients the possibility of another underlying infectious etiology for lymphoproliferative features (ie mycobacteria) should always be screened.

Among parasitic infections, Leishmaniasis presents in most of cases with marked hepato-splenomegaly and diffuse lymphadenopathy. This is often accompanied by cytopenia, which is often multilineage and dependent on direct bone marrow involvement, and elevation of serum immunoglobulin.^{8,9} On the other hand, in the immunocompetent host, toxoplasmosis presents in most of the cases with isolated cervical or occipital lymphadenopathy. However, some patients can display an EBV-like phenotype with diffuse lymphadenopathies and/or splenomegaly; in rarer cases, a chronic disease course with persistent/recurrent lymphadenopathy has been described.¹⁰

Bacterial infections usually present with lymph nodal involvement in isolated stations in the form of lymphadenitis (mostly caused by Gram-positive bacteria) with an acute course and the presence of clear localized inflammation.¹ A more subtle presentation with a subacute course is commonly associated with nontuberculous mycobacterial infections (NTM).^{11,12} In this case, the definitive diagnosis relies on the positivity of PCR or cultures on the tissue specimen/lymph nodal aspirate. However, clinical history and concordant investigations (tuberculin skin test [TST], Interferon-gamma release assay [IGRA]) could help in identifying patients with probable NTM lymphadenitis.¹¹ Rarely, infections caused by *Bartonella henselae* can cause a diffuse picture of lymphadenopathy and splenic involvement instead of the classical cat-scratch disease.^{13,14} In this case, the patient's history can significantly drive the execution of serological investigations.

Hematological Malignancies

In pediatric age, the most common cause of localized lymphoid malignancy (accounting for 60% of pediatric lymphomas) is represented by Hodgkin lymphoma (HL), which is more commonly identified in adolescents. HL presents in most of the cases with localized lymphadenopathy in lateral cervical stations (70–80%), but also axillary (10–20%) and inguinal lymph nodes can be involved.¹⁵ On the other hand, non-Hodgkin lymphomas (NHL) are a heterogeneous group with variable age at onset and clinical presentation. In NHL, lymphadenopathy is more often generalized compared to HL, and a systemic presentation with leukemia-like features is proper for lymphoblastic lymphomas.^{16–18}

Differently, although the clinical picture of hemophagocytic lymphohistiocytosis (HLH) comprehends in most of the cases lymphoproliferative features (splenomegaly, diffuse lymphadenopathy), patients experience a relevant systemic phenotype with high-grade fever and general impairment. Patients with HLH typically show elevated serum ferritin levels, elevated triglycerides, transaminases, LDH, and IL-2 receptor (IL-2R) in association with cytopenia and reduced erythrocyte sedimentation rate (ESR).¹⁹

Finally, in patients presenting with acute lymphoblastic leukemia the presence of diffuse lymphadenopathy can be frequently part of the clinical picture at disease onset, often in association with marked splenomegaly, which is commonly featured by elevated stiffness. Differently, acute myeloid leukemia and chronic leukemias are more frequently associated with splenomegaly.^{17,20,21} In patients with acute leukemia, lymphoproliferative features are generally observed in a wider context of systemic involvement (fever, malaise, weakness) and profound cytopenia. Therefore, their description goes beyond the aims of this paper.

First-Level Diagnostic Approach

In the initial diagnostic approach, anamnesis and physical examination should first focus on the identification of elements suggestive of infections. These include the acute onset, local pain and inflammation (such as soft consistency and free mobility of lymph nodes on the subcutaneous regions), and risk factors for zoonosis. In patients with clearly suspected infectious lymphoproliferation, the choice of performing laboratory investigations and/or ultrasound depends on the clinical picture and individual condition (Figure 1). However, it is pivotal to remark that, when bacterial lymphadenitis is highly suspected, prompt empirical therapy should be initiated independently from the diagnostic assessment.

Among the main warning signs to suspect malignant lymphoproliferation, the chronic and progressive course of the disease, and the association with systemic involvement (fever, weight loss, itching, night sweating) should always be investigated. However, the sensibility of these signs is limited.^{15,16} Concerning physical assessment, as a general rule, in patients with malignancy lymph nodes present enhanced consistency and are nonpainful and without mobility on the lower planes, in the absence of signs of local inflammation.²² The simultaneous presence of mediastinal enlargement is strongly suggestive of malignancy, as well as the finding of supraclavicular lymph nodes. When lymphoma is suspected, performing an abdomen ultrasound (US) and chest X-ray is mandatory to evidence the involved areas.²³ Laboratory investigations are often non-specific for the diagnosis of lymphoma. They typically show elevation of inflammatory markers (specifically, ESR), that can be associated with chronic, microcytic anemia and leukocytosis. On the other hand, the laboratory picture is generally highly suggestive in the case of acute leukemia and HLH.

Apart from laboratory investigations, the analysis of US features can significantly help in the diagnostic approach. Specifically, lymph nodes in patients with lymphoma have usually a round shape, anechoic or hypoechoic structure, peripheral vascularization, and absence of hilum. Differently, reactive lymph nodes usually show an ovoid shape and well-defined cortical differentiation and hilum²⁴ (Figure 2). Also, the US assessment of the spleen could give important elements. The finding of markedly altered spleen texture is an element of suspicion for an underlying malignancy, as well as the presence of focal, non-cystic lesions. Multiple focal spleen lesions can also be observed in some specific infectious diseases, such as bartonellosis^{13,25} (Figure 3).

Finally, lymph nodal biopsy should be reserved for patients with a high risk of lymphoma based on the clinical and laboratory assessment and patients with persistent lymphoproliferation without a definite cause.²⁶ Excisional biopsy represents the gold standard for the diagnosis of lymphomas and has a greater sensibility and specificity compared with core needle biopsy and fine needle aspiration cytology (FNAC).^{27–30} Lymph nodal excision, with a diagnostic and

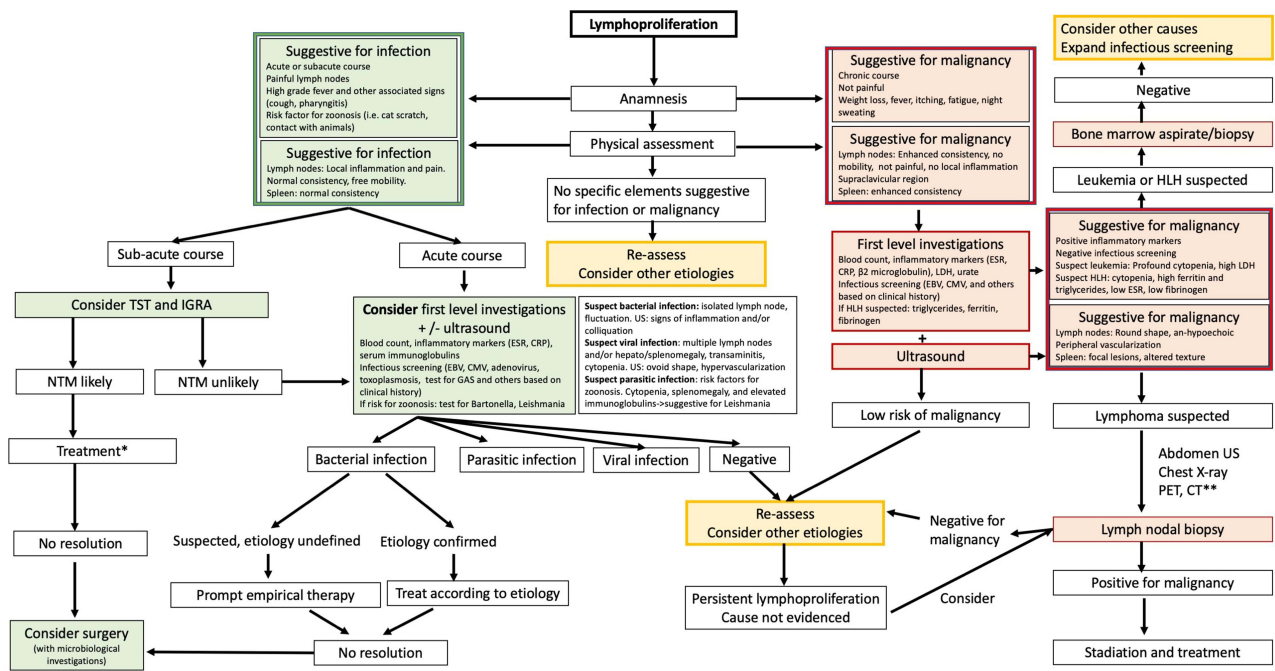


Figure 1 First-level approach to patients presenting with lymphoproliferation.

Notes: This algorithm identifies the patients with a clinical picture suggestive for infection (green boxes) and malignancy (red boxes) and those with a less defined clinical picture (yellow boxes). The diagnostic approach for patients with suspected infection or malignancy is provided, evidencing that first-level analysis and US imaging are mandatory in patients with high risk of malignancy. On the other hand, when infection is suspected, the choice about performing laboratory and imaging investigations relies on the individual situation. Patients without a clearly defined diagnosis should be periodically re-assesses and eventually undergo further investigations. *There is no uniform consensus regarding the need to perform prolonged antibiotic treatment in NTM lymphadenitis, and some authors suggest to perform only clinical observation. **PET and CT can be performed also before lymph nodal biopsy based on the clinical judgement.

Abbreviations: CMV, Cytomegalovirus; CRP, C-reactive protein; CT, Computed tomography; EBV, Epstein-Barr virus; ESR, Erythrocyte sedimentation rate; GAS, Group A Streptococcus, HLH, Hemophagocytic lymphohistiocytosis; IGRA, Interferon-gamma release assay; NTM, Nontuberculous mycobacteria; PET, Positron emission tomography; TST, tuberculin skin test; US, Ultrasound.

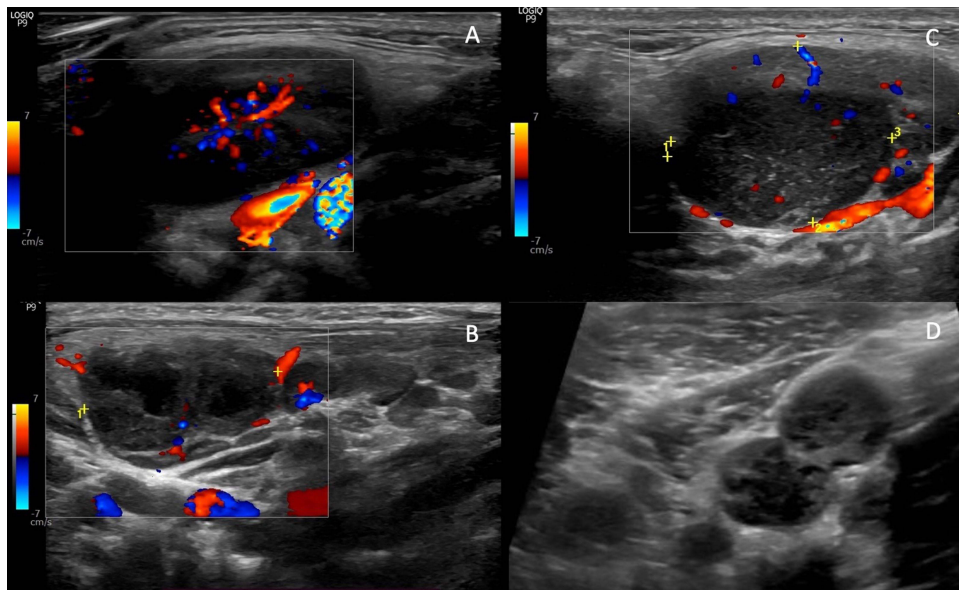


Figure 2 US findings in lymphadenopathies with different etiology.

Notes: (A) Reactive lymphadenopathy in a patients with acute respiratory infection. Lymph nodes are typically featured by ovoid shape, clear evidence cortical differentiation, and hilar vascularization; (B) Bacterial lymphadenitis, in which some areas of colliquation are evident; (C) Lymph nodes in a patient with Hodgkin lymphoma. Lymph nodes are featured by round shape, hypo-anechoic texture, absence of cortical differentiation, and scarce, peripheral vascularization; (D) Lymph nodes in a patient with immune dysregulation and granulomatous lymphadenitis. In this condition, lymph nodes can show some overlapping features with malignancies, including round shape, hypoechoic texture, and irregular vascularization.

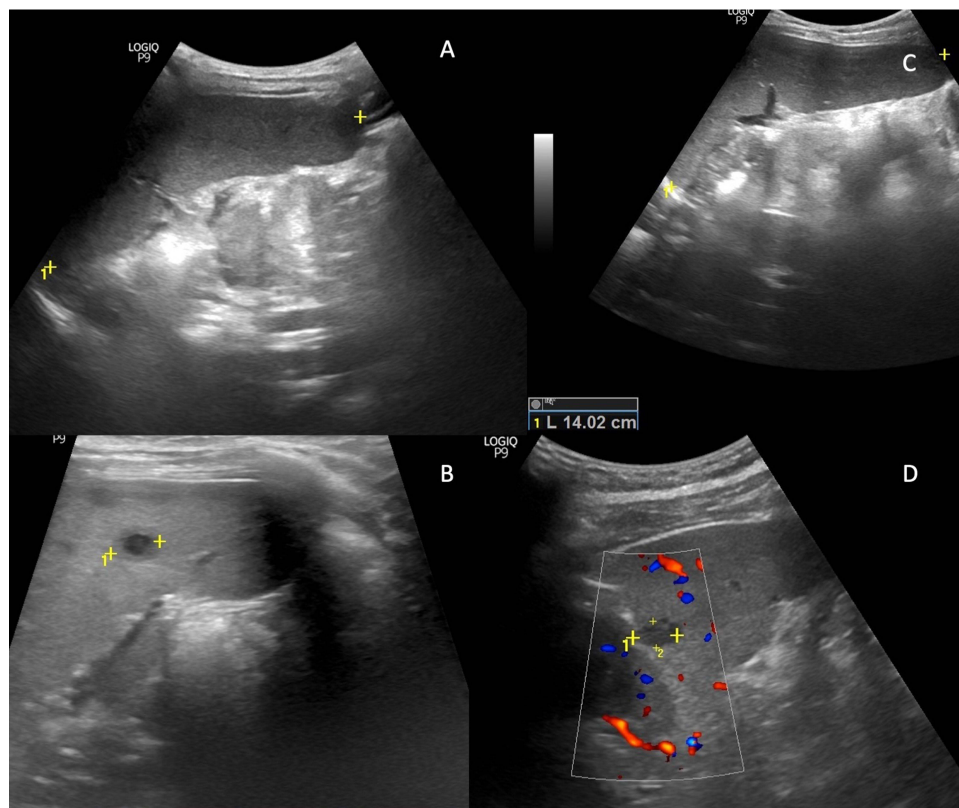


Figure 3 US findings in splenomegaly with different etiology.

Notes: (A) Splenomegaly in a patient with acute EBV infection, featured by a mildly disomogeneous texture and absence of focal lesions; (B) Focal spleen lesion in a patient with *Bartonella henselae* infection. In this condition, the lesions are usually multiple and anechoic, but during the disease evolution a peripheral hypoechoic are can be detected; (C) Splenomegaly in a patient with Gaucher disease, featured by homogeneous spleen texture (D) Spleen involvement in Hodgkin lymphoma, in which focal hypoanechoic lesions are evident.

therapeutic function, could also be necessary for patients with refractory bacterial lymphadenitis and/or colliquative evolution.¹² This is particularly relevant for patients with NTM disease, in which lymph nodal excision, when feasible,¹¹ is associated with a higher resolution rate compared with incision or drainage.^{31,32}

What is Less Common: Lymphoproliferative Features in Inborn Errors of Metabolism

Splenomegaly, hepatomegaly, and lymphadenopathy, usually accompanied by cytopenia, can be found as suggestive features of IEM. Specifically, they can be frequently evidenced in lysosomal storage diseases such as Gaucher disease (GD) and Niemann-Pick disease (NPD). Although in these conditions the disease mechanism is not directly linked to lymphocyte proliferation but depends on the accumulation of metabolites, the clinical features show significant similarities with hematologic disorders. Therefore, their recognition by hematologists is essential to promptly drive the diagnostic process.

GD is a rare autosomal recessive disorder caused by mutations in the *GBA1* gene, located on chromosome 1 (1q21). The molecular defect leads to a decreased activity of the lysosomal enzyme beta glucocerebrosidase (GC-ase), which conducts the storage of glucocerebroside and other glycolipids in various tissues, such as bone marrow, spleen, and liver.^{33,34}

Three major clinical types of this rare disease have been identified: Type-1 GD, which is the most common, and types 2 and 3, which are less common and also associated with neurological impairment.³³ Type 1 GD is the most prevalent form in the Western world; at diagnosis, patients present with several hematological signs, including splenomegaly, anemia, and thrombocytopenia. They can also show bone disease, which is featured by bone deformities (such as the Erlenmeyer flask deformity in the distal meta-diaphyseal region of the femur), reduced bone density, and bone necrosis.³⁵

It has been shown that splenomegaly is present in 95% of children affected by type 1 GD, appearing earlier than other manifestations. Specifically, in children with GD aged less than 6 years splenomegaly is present in 99% of the cases, and in half of these it can be the only clinical sign at diagnosis.^{34,36} Additionally, hepatomegaly is noted in 60–80% of

patients.³³ The prevalence of lymphadenopathy in GD is difficult to establish due to the paucity of data. Results from a study search³⁷ suggest that the most commonly diagnosed lymphadenopathies are mesenteric and/or mediastinal (29 cases), although cases of cervical/axillary, supraclavicular, and generalized lymphadenopathy are also reported. For the mentioned reasons, patients are often first addressed for hematological evaluation. However, it has been reported that GD and other IEM are not often considered by hematologists and oncologists in the differential diagnosis of patients presenting with lymphoproliferative features.³⁴

In addition to the clinical findings previously described, several other clinical and laboratory findings are useful criteria that can lead to performing the GC-ase enzyme assay, without first subjecting children to bone marrow aspirate/biopsy. Considering radiologic evidence of bone disease, which is present in most children with GD at diagnosis (81%),³⁴ could shorten the diagnostic process. Similarly, some biomarkers available in any clinical chemistry laboratory should be assessed if we are presented with thrombocytopenia and/or anemia in children with splenomegaly.³⁴ As demonstrated in the literature, tartrate-resistant acid phosphatase (TRAP) and ferritin are frequently elevated in patients with GD and can also be associated with disease severity. Ferritin levels may be predictive of the onset of bone complications and are frequently associated with splenectomy.^{33,38}

The diagnosis of GD must be confirmed by establishing deficient GC-ase activity in total leukocytes, mononuclear cells, or cultured fibroblasts. The residual enzyme activity is usually approximately 10–15% of the normal value.^{33,39} Dried blood spots can also be used for the first-level enzymatic assay. Indeed, this method has been demonstrated to be effective in identifying patients with GD among those presenting to hematological attention for the presence of splenomegaly and/or thrombocytopenia. If the diagnosis of GD is confirmed, genetic molecular diagnosis is mandatory to identify the risk of the chronic neuronopathic form of GD and to determine the appropriate follow-up.³⁴

Concerning NPD, splenomegaly and hepatomegaly are described in a high percentage of patients with type A and type B NPD, which are autosomal recessive diseases caused by a deficiency of the enzyme acid sphingomyelinase (ASM).⁴⁰ In patients with type A NPD, children present with hepatosplenomegaly in the first months of life, in association with growth failure, progressive hypotonia, and severe neurological impairment. About half of the patients show a macular cherry-red spot, that could help in reaching an earlier diagnosis.⁴¹ Also patients with type 2 NPD present with early hepatosplenomegaly associated with neurological impairment. They also have an increased risk for severe cardiac abnormalities, respiratory infections, respiratory failure, and liver failure.⁴² First-level laboratory assessment, although non-specific, often shows cytopenia with progressive worsening and dyslipidemia with reduced HDL cholesterol and increased LDL cholesterol and triglycerides. The diagnosis of NPD requires the enzymatic analysis demonstrating reduced ASM activity and the genetic confirmation evidencing mutations in the SMPD1 gene.⁴⁰

What is New: Lymphoproliferation in Inborn Errors of Immunity

The presentation with lymphadenopathy, usually with chronic or relapsing disease course and variably associated with splenomegaly, hepatomegaly, or organ involvement, is described in a wide range of IEI (Table 1). These include well-known entities such as common variable immunodeficiency (CVID), combined immunodeficiencies, and disorders with prominent immune dysregulation, in which the autoimmune lymphoproliferative syndrome (ALPS) is the most studied. Also, lymphoproliferative features are frequently observed in diseases caused by an altered control of specific infections, as evidenced in EBV-related disorders.^{2,3,43}

CVID is associated with lymphoproliferation in more than 10% of the patients. The incidence is specifically higher in patients carrying definite genetic mutations, including NFKB1 and TACI.^{3,44,45} As the genetic background of CVID is partly unexplored and extremely heterogeneous, a unique inheritance pattern is not defined. In patients with autosomal dominant mutations, a positive familial history of antibody deficiency could help in the diagnostic approach.⁴⁶ According to current diagnostic criteria, CVID can be defined by the presence of hypogammaglobulinemia (IgG and IgA or IgM with values below two standard deviations for age) associated with impaired B cell maturation, which is demonstrated by low levels of switched memory B cells or impaired humoral specific response. To diagnose CVID, patients must be at least 3 years of age and should not exhibit a significant T cell deficiency.⁴⁷ In the heterogeneous clinical expression of CVID, most of the patients present to clinical attention for recurrent sinopulmonary infections, which can also cause the development of bronchiectasis. However, a variable percentage of patients could present with isolated features of autoimmunity (mainly,

Table I Inborn Errors of Immunity Associated with Lymphoproliferation

Immune dysregulation disorders	<ul style="list-style-type: none"> - Autoimmune lymphoproliferative syndrome: ALPS-FAS, ALPS-FASL, ALPS-sFAS, ALPS-casp10, ALPS-U - Disorders of regulatory T cells: CTLA4 deficiency, LRBA deficiency, STAT3 GOF, STAT1 GOF, BACH2 deficiency, CD25 deficiency) - EBV-related disorders: X-linked proliferative syndromes, XMEN syndrome, CD70 deficiency, CD27 deficiency, ITK deficiency, RASGRP1 deficiency, CTPSI deficiency, STK4 deficiency) - Protein kinase C δ deficiency(PKCD)
Primary antibody deficiencies	<ul style="list-style-type: none"> - Common variable immunodeficiency - Activated phosphoinositide 3-kinase δ syndrome: APDS I, APDS2, APDS-L
Combined immunodeficiencies	<ul style="list-style-type: none"> - RAG-associated disorders: Omenn syndrome, hypomorphic RAG1 and RAG2 mutations - Other combined immunodeficiencies: diseases of CARD11-BCL10-MALT1 axis, ILR2β deficiency
Others	<ul style="list-style-type: none"> - Phenocopies of IEI: RAS-associated leukoproliferative disease (RALD) - Diseases with susceptibility to lymphoid neoplasms: ataxia-telangiectasia, Nijmegen breakage syndrome, Bloom syndrome

autoimmune cytopenia), lymphoproliferation, or inflammatory bowel disease (IBD)-like enteropathy.⁴⁸ Moreover, patients with CVID can develop pulmonary lymphoproliferation in the form of granulocytic lymphocytic interstitial lung disease (GLILD), which is associated with a significant increase in morbidity and mortality.^{45,49}

Hematologic autoimmunity and lymphoproliferation are the most common clinical signs of disease presentation in patients with ALPS. In this condition, mutations impairing the functioning of the FAS-mediated apoptotic pathway (FAS, FAS ligand, caspase 10) led to the accumulation of $\alpha\beta$ double-negative T lymphocytes ($\alpha\beta$ DNTs) and self-reactive lymphocytes.^{50,51} Consequently, the vast majority of the patients develop chronic, diffuse lymphadenopathy, hepato-splenomegaly, and autoimmune cytopenia.⁵⁰ To diagnose ALPS, the presence of autoimmune cytopenia or chronic lymphoproliferation is required in association with the positivity of ALPS-associated serum markers. These include the elevation of $\alpha\beta$ DNTs, soluble FAS ligand, serum vitamin B12, interleukin (IL)-10 and IL-18, and impaired FAS-dependent apoptosis.⁵² The inheritance pattern of ALPS is not homogeneous, as the disease can be transmitted with both autosomal dominant and recessive patterns.⁵¹

The advances in the knowledge of immune dysregulation disorders allowed to identify new monogenic entities that can present with features partially overlapping ALPS and CVID. These conditions include disorders of regulatory T cells (Tregopathies), such as CTLA-4 deficiency, LRBA deficiency, and STAT-associated disorders, as well as combined immunodeficiencies and disorders of lymphocyte proliferation.^{53,54} Recently, the definition of autoimmune lymphoproliferative disorders (ALPID) has been proposed to identify this wide range of complex phenotypes encompassing autoimmunity and lymphoproliferation.⁵⁵

Concerning Tregopathies, the clinical phenotype of CTLA-4 and LRBA deficiency present significant analogies, as the pathogenesis is partially overlapping. Specifically, both diseases are associated with a clinical picture of combined immunodeficiency with increased susceptibility to infections, autoimmunity (cytopenia, endocrinopathy, arthritis, uveitis), and lymphoproliferation, which includes also the possibility of developing GLILD and lymphomas.^{54,56} Among STAT-associated disorders, the highest rate of lymphoproliferative manifestations is described in patients with STAT-3 gain of function (GOF) mutation. In this rare disease, more than 70% of the patients develop lymphoproliferative features at disease onset and during follow-up, and this represents the most common disease sign, as observed in large cohort studies. Other clinical signs are represented by autoimmune cytopenia (about 60% of the patients), severe eczema, enteropathy, and other autoimmune conditions, mainly enteropathy.⁵⁷ The laboratory findings in patients with Tregopathies are variable and non-specific and include hypogammaglobulinemia and altered B and T cell homeostasis, which can configure CVID-like or ALPS-like features.^{3,54}

Two paradigmatic examples of disorders affecting both humoral and cellular immunity are represented by the activated phosphoinositide 3-kinase δ syndrome (APDS) and the protein kinase C δ deficiency (PKCD).^{53,54} Lymphoproliferative features are also a hallmark of other combined immunodeficiencies, such as those depending on RAG mutations (Omenn

syndrome in newborns and infants, RAG hypomorphic mutations in children and adolescents) and diseases affecting the CARD11-BCL10-MALT1 complex.^{58,59}

APDS is caused by mutations that are responsible for the uncontrolled activation of the phosphoinositide-3-kinase (PI3K)-dependent molecular pathways, including the events associated with mTOR signaling. This causes a higher lymphocyte proliferative rate and immune dysfunction. APDS patients have a peculiar immunological asset, featured by increased CD57-positive senescent T CD8+ cells and transitional B cells in most of the cases associated with hypogammaglobulinemia.⁶⁰ The disease is clinically expressed with a combination of infectious susceptibility, involving both sinopulmonary bacterial infections and herpesvirus infections, and immune dysregulation.^{61,62} Specifically, patients with APDS show lymphoproliferative features in more than half of the cases, and more than 10% of the patients develop hematological malignancies.^{60,61}

As therapeutic agents targeting the specific molecular defect are available for some of the described conditions (ALPS, APDS, STAT3 GOF, CTLA-4 deficiency, and LRBA deficiency), providing the early diagnosis of IEI in a patient presenting with lymphoproliferation is of significant clinical relevance.⁶³

Lymphoproliferation Caused by Other Etiologies

Among the rare diseases to be considered in the differential diagnosis of pathologic conditions presenting with lymphoproliferative manifestations, sarcoidosis and Castleman should be considered.

Sarcoidosis is a disease featured by a typical finding of symmetrical hilar pulmonary adenopathy associated with peripheral lymphoproliferation (lymphadenopathies, splenic involvement) and autoimmune manifestations, which include arthritis, uveitis, and others.⁶⁴ In patients with sarcoidosis, the histopathological exam typically shows non-caseating sterile granulomas. Serum angiotensin-converting enzyme (sACE) is usually increased (30–80% of the patients), as the result of the enhanced macrophage activation, although this marker is not highly sensitive and specific.⁶⁴ Notably, in pediatric age, a sarcoidosis-like disease is found in patients with Blau syndrome. This condition is characterized by the classic triad of arthritis, uveitis, and dermatitis in association with lymphadenopathy.⁶⁵

Castleman disease is defined by the presence of lymph nodal involvement with peculiar histologic features, such as follicles with germinal center involution, marked capillary proliferation, and follicular and interfollicular endothelial hyperplasia.⁶⁶ The disease can present as unicentric, and generally idiopathic, or multicentric, which is often dependent on HHV8 infection. In patients with multicentric disease, the lymphoproliferative features can be accompanied by cytopenia, autoimmune diseases, hemophagocytosis, and other organ involvement.⁶⁷ In the case of Castleman disease, the lymph nodal biopsy is a pivotal step to confirm the diagnosis. Therefore, when the disease is suspected and histopathology is not conclusive, imaging investigations (CT, PET) are needed to identify the lymph nodal stations with a higher probability of being representative for a second biopsy.⁶⁶

Moreover, lymphoproliferation can be observed in patients with systemic autoimmune diseases, including systemic lupus erythematosus and dermatomyositis. In these conditions, lymphoproliferative features are often accompanied by the involvement of other systems, evidenced by musculoskeletal symptoms, arthritis, cutaneous manifestations, and renal involvement.⁶⁸ Other rare conditions presenting with lymphoproliferation include IgG4-associated disease, histiocytosis, and Kikuchi-Fujimoto disease, which is typically featured by subacute necrotizing lymphadenopathy.^{69–71}

Finally, in patients with recurrent episodes of lymphoproliferation, especially if associated with fever and laboratory features of hyperinflammation, the possibility of an underlying autoinflammatory disease should be considered. Children with the periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome can present with isolated recurrent febrile lymphadenopathy, in the absence of the other disease signs. In this case, the timing of recurrence is a significant help for differential diagnosis.^{72,73} Similarly, the febrile episodes in patients with mevalonate kinase deficiency are often featured by recurrent lymphadenopathy, which can also be associated with hepatosplenomegaly.⁷⁴

Pathogenic and Clinical Overlaps: Inborn Errors of Immunity, Infections, and Malignancies

The immune dysregulation underlying IEI is also responsible for an enhanced susceptibility to viral infections, which can itself result in uncontrolled lymphoproliferation. Also, patients show an higher risk of developing malignant diseases, particularly lymphoid malignancies (Figure 4).

A paradigmatic example is represented by the class of EBV-associated disorders. In these conditions, molecular defects impairing the immune response against viruses, and specifically EBV (lymphocyte proliferation, co-stimulation, pathogen clearance) are responsible for the uncontrolled viral proliferation.⁷⁵ The association between the lymphoproliferative features and the viral infection could be demonstrated by performing the analysis of EBV-encoded small RNAs (EBER) on tissue specimens. Moreover, these conditions carry an elevated risk of EBV-associated lymphomas, which are cumulatively described in more than half of the patients. In some specific conditions, such as the X-linked proliferative syndrome 1 (XLP-1) and others, the molecular defect is also associated with the potential development of HLH following viral infection.^{75,76}

Apart from EBV-associated disorders, most IEs are associated with an increased risk of lymphoid malignancies. Indeed, lymphomas account for more than 60% of the neoplastic diseases observed in this subset of patients.⁷⁷ This depends on multiple mechanisms, including impaired tumor surveillance, uncontrolled lymphocyte proliferation, and ineffective apoptosis. Additionally, some specific conditions are featured by impaired DNA repair and stability, thus being associated with a high risk of lymphoid and extra-lymphoid neoplasia.⁷⁸ The development of lymphomas is described with higher frequency in patients diagnosed with ALPS (51-fold higher risk of HL), APDS, antibody deficiencies, and IEI associated with impaired DNA repair, such as ataxia-telangiectasia, NBS, and Bloom syndrome.^{77,79,80}

Finally, it is important to underline that the histopathological characterization of lymphadenopathies or tissues involved by lymphoproliferation belonging to patients affected by IEI is a relevant challenge. Indeed, these histologic specimens can show some sarcoidosis-like or Castleman-like aspects, as well as marked lymph nodal disruption mimicking malignancies.⁸¹ Similarly, the radiological features of lymph nodes and spleen of patients with IEI often show elements that suggest a potential diagnosis of malignancies, such as altered tissue echogenicity, texture, and density. Therefore, the interpretation of pathological and radiological findings in patients with diagnosed or suspected IEI requires extensive critical reasoning, specific experience, and close cooperation with clinicians with immunological expertise.

Practical Aspects and Diagnostic Implications

The diagnostic approach to pediatric patients with lymphoproliferation in routinely clinical practice is markedly heterogeneous. To be comprehensive, it must include a broad range of differential diagnoses, in order not to under-diagnose non-infectious conditions. From a clinical point of view, as previously discussed, the most relevant first approach to a patient with lymphoproliferation is to search for the main features associated with infections and

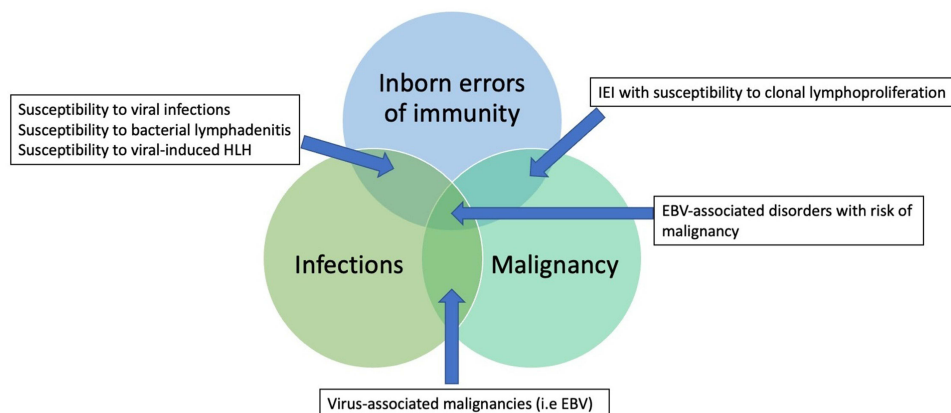


Figure 4 Overlaps in the pathogenesis of lymphoproliferation in IEI, infections, and malignancies.

malignancies. After this first diagnostic step has reasonably excluded these two conditions, in patients with persistent lymphoproliferative features the search for other underlying causes is mandatory.

In patients with persistent lymphoproliferation, lymph nodal biopsy is often performed during the initial diagnostic assessment. This can lead to the identification of specific diagnoses based on the histologic features, including Castleman disease and, when the clinical history is consistent, sarcoidosis. On the other hand, when the biopsy is not suggestive of a specific diagnosis or not performed, an in-depth analysis is necessary. For this purpose, the investigation of personal and familial history and the search for specific associated signs are of primary importance (Figure 5). The history of recurrent lymphadenopathy associated with febrile episodes is highly suggestive for the diagnosis of autoinflammatory disorders. On the other hand, the association with cutaneous rash, arthritis, or muscle pain can orient toward systemic connective tissue diseases and lead to the analysis of specific autoantibodies and inflammatory markers (ESR, serum complement levels, and others) based on the clinical picture.

To suspect an underlying IEI, positive familial history of autoimmunity, infections, or lymphoproliferation, as well as a personal history of severe infections or other signs of immune dysregulation (autoimmunity, especially cytopenia and endocrinopathy, enteropathy, and eczema) are relevant warning signs. In this category of patients, a baseline immunological assessment should be performed. This first-level assessment should include the analysis of full blood count, serum immunoglobulin, lymphocyte subpopulations, and the dosage of vitamin B12.³ When the clinical history and first-level analysis are suggestive, the determination of αβDNTs, serum IL-10 and IL-18, and the analysis of apoptotic function can be performed to guide towards the diagnosis of ALPS. Differently, the analysis of switched memory B cells and specific humoral response (measurable by determining the response to vaccinations) can allow the diagnosis of CVID.³ The elevation of CD57 is useful

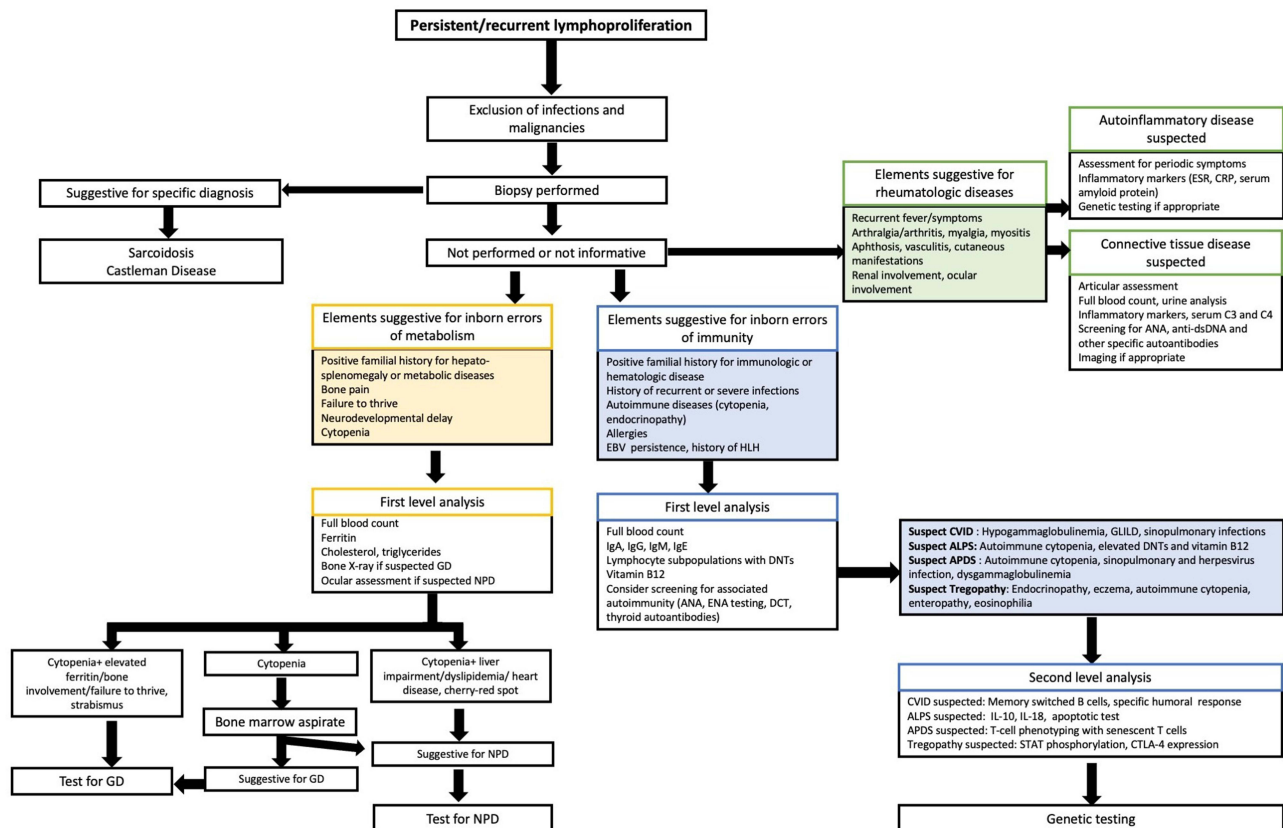


Figure 5 Diagnostic algorithm for the identification of rare causes of lymphoproliferation.

Notes: In patients with persistent/recurrent lymphoproliferation, when a diagnosis has not been reached, the search for signs associated with IEI (blue boxes), IEM (yellow boxes), and rheumatologic diseases (green boxes) could lead to appropriate investigations, and finally to the identification of rare etiologies underlying lymphoproliferation. **Abbreviations:** APDS, activated phosphoinositide 3-kinase δ syndrome; ALPS, Autoimmune lymphoproliferative syndrome; ANA, Antinuclear antibodies; CVID, Common variable immunodeficiency; DCT, Direct Coombs test; EBV, Epstein-Barr virus; ENA, extractable nuclear antigen; GD, Gaucher disease; GLILD, Granulomatous lymphocytic interstitial lung disease; HLH, Hemophagocytic lymphohistiocytosis; IEI, Inborn errors of immunity, IEM, Inborn errors of metabolism; NPD, Niemann-Pick diseases.

to further enhance the suspicion of APDS, while the analysis of STAT phosphorylation, as well as the flow cytometric analysis of CTLA-4 expression, can be performed in case of specific suspect of STAT-related disorders or CTLA4/LRBA deficiency, respectively. Notably, as the clinical phenotype of the main IEI associated with lymphoproliferation presents significant overlapping, genetic testing is often necessary to establish a definitive molecular diagnosis.

To promptly identify patients with IEM, anamnesis should focus on familial history and on the presence of failure to thrive, bone pain, and neurodevelopmental delay. The association between hepato-splenomegaly and cytopenia, in the absence of other potential etiologies, deserves to be investigated for an underlying GD. Concerning this, the elevation of serum ferritin, as well as the demonstration of bone involvement (ie Erlenmeyer deformity) represent highly suggestive signs that should lead to performing the enzymatic testing.³⁴ On the other hand, when other Gaucher-associated signs are not evident, bone marrow aspirate could be necessary to rule out other potential etiologies and to allow the identification of Gaucher cells. These are typically defined by large macrophages with eccentric nuclei, abundant blue-gray cytoplasm, and wrinkled tissue paper appearance.⁸² Concerning NPD, the most well-recognized associated signs are severe neurological involvement, the finding of dyslipidemia, and macular abnormalities (cherry-red spot).⁴⁰ Also in patients with NPD, the analysis of bone marrow could identify cells with specific features, which include sea blue histiocytes and large macrophages with foamy cytoplasm and numerous small vacuoles.^{83,84}

The differential diagnosis between IEI and IEM could be challenging in some patients. Some studies show that patients with GD may present immune-dysregulation features that can overlap with APS and ALPS-like disorders, including higher counts of $\alpha\beta$ DNTs and an immune-dysregulation pattern secondary to a FAS-mediated defect of apoptosis. For these reasons, some common clinical features of both disorders, such as thrombocytopenia and splenomegaly, should be evaluated not only as an overlapping sign of different conditions but also as a result of a common pathogenic pathway impaired by different causes.⁸⁵

Conclusion and Future Directions

The etiology of lymphoproliferative features in pediatric age is extremely wide and goes far beyond the most common entities such as infectious diseases and hematological malignancies. In patients with persistent lymphoproliferation without an established diagnosis, critical reasoning based on the identification of specific warning signs and first-level analyses can significantly help in the recognition of rare disorders, including IEI and metabolic disorders. For this purpose, we have developed an algorithm in an attempt to guide the intriguingly complex process of differential diagnosis. Due to the heterogeneous spectrum of clinical presentation, close cooperation between pediatric hematologists, infectious disease and metabolic disease physicians, and immunologists is pivotal to approaching patients with unexplained lymphoproliferation and finally identifying the correct diagnostic approach for the single patient.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Pecora F, Abate L, Scavone S, et al. Management of Infectious Lymphadenitis in Children. *Children*. 2021;8(10):860. doi:10.3390/children8100860
2. Sharma S, Paliana RK, Anjani G, et al. Lymphoproliferation in inborn errors of immunity: the eye does not see what the mind does not know. *Front Immunol*. 2022;13:856601. doi:10.3389/fimmu.2022.856601
3. Costagliola G, Consolini R. Lymphadenopathy at the crossroad between immunodeficiency and autoinflammation: an intriguing challenge. *Clin Exp Immunol*. 2021;205(3):288–305. doi:10.1111/cei.13620
4. Teke Kisa P, Arslan N. Inborn errors of immunity and metabolic disorders: current understanding, diagnosis, and treatment approaches. *J Pediatr Endocrinol Metab*. 2020;34(3):277–294. doi:10.1515/jpem-2020-0277

5. Deosthali A, Donches K, DelVecchio M, Aronoff S. Etiologies of pediatric cervical lymphadenopathy: a systematic review of 2687 subjects. *Glob Pediatr Health*. 2019;6:2333794X19865440. doi:10.1177/2333794X19865440
6. Dunmire SK, Verghese PS, Balfour HH. Primary Epstein-Barr virus infection. *J Clin Virol*. 2018;102:84–92. doi:10.1016/j.jcv.2018.03.001
7. Glushko T, He L, McNamee W, Babu AS, Simpson SA. HIV lymphadenopathy: differential diagnosis and important imaging features. *AJR Am J Roentgenol*. 2021;216(2):526–533. doi:10.2214/AJR.19.22334
8. Burza S, Croft SL, Boelaert M. Leishmaniasis. *Lancet*. 2018;392(10151):951–970. doi:10.1016/S0140-6736(18)31204-2
9. van Griensven J, Diro E. Visceral leishmaniasis: recent advances in diagnostics and treatment regimens. *Infect Dis Clin North Am*. 2019;33(1):79–99. doi:10.1016/j.idc.2018.10.005
10. Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet*. 2004;363(9425):1965–1976. doi:10.1016/S0140-6736(04)16412-X
11. Roy CF, Balakrishnan K, Boudewyns A, et al. International pediatric otolaryngology group: consensus guidelines on the diagnosis and management of non-tuberculous mycobacterial cervicofacial lymphadenitis. *Int J Pediatr Otorhinolaryngol*. 2023;166:111469. doi:10.1016/j.ijporl.2023.111469
12. Kuntz M, Kohlfürst DS, Feiterna-Sperling C, et al. NTMkids Consortium. Risk factors for complicated lymphadenitis caused by nontuberculous mycobacteria in children. *Emerg Infect Dis*. 2020;26(3):579–586. doi:10.3201/eid2603.191388
13. Tirotta D, Mazzeo V, Nizzoli M. Hepatosplenic cat scratch disease: description of two cases undergoing contrast-enhanced ultrasound for diagnosis and follow-up and systematic literature review. *SN Compr Clin Med*. 2021;3(10):2154–2166. doi:10.1007/s42399-021-00940-1
14. Dhal U, Hicklen RS, Tarrand J, Kontoyiannis DP. Cat scratch disease as a mimicker of malignancy. *Open Forum Infect Dis*. 2021;8(11):ofab500. doi:10.1093/ofid/ofab500
15. Lo AC, Dieckmann K, Pelz T, et al. Pediatric classical Hodgkin lymphoma. *Pediatr Blood Cancer*. 2021;68:e28562. doi:10.1002/pbc.28562
16. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. *Lancet*. 2012;380(9844):848–857. doi:10.1016/S0140-6736(12)60605-9
17. Burkhardt B, Hermiston ML. Lymphoblastic lymphoma in children and adolescents: review of current challenges and future opportunities. *Br J Haematol*. 2019;185(6):1158–1170. doi:10.1111/bjh.15793
18. Kline KAF, Kallen ME, Duong VH, Law JY. Acute lymphoblastic leukemia and acute lymphoblastic lymphoma: same disease spectrum but two distinct diagnoses. *Curr Hematol Malig Rep*. 2021;16(5):384–393. doi:10.1007/s11899-021-00648-y
19. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. *Blood*. 2020;135(16):1332–1343. doi:10.1182/blood.2019000936
20. Inaba H, Mullighan CG. Pediatric acute lymphoblastic leukemia. *Haematologica*. 2020;105(11):2524–2539. doi:10.3324/haematol.2020.247031
21. Ibrahimova A, Pommert L, Breese EH. Acute Leukemia in Infants. *Curr Oncol Rep*. 2021;23(3):27. doi:10.1007/s11912-021-01021-1
22. Mohseni S, Shojafard A, Khorgami Z, Alinejad S, Ghorbani A, Ghafouri A. Peripheral lymphadenopathy: approach and diagnostic tools. *Iran J Med Sci*. 2014;39(2 Suppl):158–170.
23. McCarten KM, Nadel HR, Shulkin BL, Cho SY. Imaging for diagnosis, staging and response assessment of Hodgkin lymphoma and non-Hodgkin lymphoma. *Pediatr Radiol*. 2019;49(11):1545–1564. doi:10.1007/s00247-019-04529-8
24. Vaughn JA. Imaging of Pediatric Cervical Lymphadenopathy. *Neuroimaging Clinics of North America*. 2023;33(4):581–590. doi:10.1016/j.nic.2023.05.008
25. Caremani M, Occhini U, Caremani A, et al. Focal splenic lesions: US findings. *Journal of Ultrasound*. 2013;16(2):65–74. doi:10.1007/s40477-013-0014-0
26. Locke R, Comfort R, Kubba H. When does an enlarged cervical lymph node in a child need excision? A systematic review. *Int J Pediatr Otorhinolaryngol*. 2014;78(3):393–401. doi:10.1016/j.ijporl.2013.12.011
27. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059–3067. doi:10.1200/JCO.2013.54.8800
28. Shanbhag S, Ambinder RF. Hodgkin lymphoma: a review and update on recent progress. *CA Cancer J Clin*. 2018;68(2):116–132. doi:10.3322/caac.21438
29. Gonçalves MDC, de Oliveira CRG, Sandes AF, et al. Core needle biopsy in lymphoma diagnosis: the diagnostic performance and the role of the multidisciplinary approach in the optimization of results. *Am J Surg Pathol*. 2023;47(1):111–123. doi:10.1097/PAS.0000000000001991
30. Campanelli M, Cabry F, Marasca R, Gelmini R. Peripheral lymphadenopathy: role of excisional biopsy in differential diagnosis based on a five-year experience. *Minerva Chir*. 2019;74(3):218–223. doi:10.23736/S0026-4733.18.07752-0
31. Neven Q, Van der Linden D, Hainaut M, Schmitz S. Long-term outcome of surgical excision for treatment of cervicofacial granulomatous lymphadenitis in children. *Eur Arch Otorhinolaryngol*. 2020;277(6):1785–1792. doi:10.1007/s00405-020-05880-5
32. Zimmermann P, Tebruegge M, Curtis N, Ritz N. The management of non-tuberculous cervicofacial lymphadenitis in children: a systematic review and meta-analysis. *J Infect*. 2015;71(1):9–18. doi:10.1016/j.jinf.2015.02.010
33. Stirnemann J, Belmatoug N, Camou F, et al. A review of gaucher disease pathophysiology, clinical presentation and treatments. *Int J Mol Sci*. 2017;18(2):441. doi:10.3390/ijms18020441
34. Di Rocco M, Andria G, Deodato F, Giona F, Micalizzi C, Pession A. Early diagnosis of Gaucher disease in pediatric patients: proposal for a diagnostic algorithm. *Pediatr Blood Cancer*. 2014;61(11):1905–1909. doi:10.1002/pbc.25165
35. Motta I, Consonni D, Stroppiano M, et al. Splenomegaly Gaucher group. Predicting the probability of Gaucher disease in subjects with splenomegaly and thrombocytopenia. *Sci Rep*. 2021;11(1):2594. doi:10.1038/s41598-021-82296-z
36. Kaplan P, Andersson HC, Kacena KA, Yee JD. The clinical and demographic characteristics of nonneuropathic Gaucher disease in 887 children at diagnosis. *Arch Pediatr Adolesc Med*. 2006;160(6):603–608. doi:10.1001/archpedi.160.6.603
37. Ramaswami U, Mengel E, Berrah A, et al. Throwing a spotlight on under-recognized manifestations of Gaucher disease: pulmonary involvement, lymphadenopathy and Gaucheroma. *Mol Genet Metab*. 2021;133(4):335–344. doi:10.1016/j.ymgme.2021.06.009
38. Stirnemann J, Belmatoug N, Vincent C, Fain O, Fantin B, Mentre F. Bone events and evolution of biologic markers in Gaucher disease before and during treatment. *Arthritis Res Ther*. 2010;12(4):R156. doi:10.1186/ar3111
39. Neufeld EF. Lysosomal storage diseases. *Annu Rev Biochem*. 1991;60(1):257–280. doi:10.1146/annurev.bi.60.070191.001353
40. Schuchman EH, Desnick RJ. Types A and B Niemann-Pick disease. *Mol Genet Metab*. 2017;120(1–2):27–33. doi:10.1016/j.ymgme.2016.12.008
41. McGovern MM, Aron A, Brodie SE, Desnick RJ, Wasserstein MP. Natural history of Type A Niemann-Pick disease: possible endpoints for therapeutic trials. *Neurology*. 2006;66(2):228–232. doi:10.1212/01.wnl.0000194208.08904.0c

42. Cassiman D, Packman S, Bembi B, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): literature review and report of new cases. *Mol Genet Metab.* 2016;118(3):206–213. doi:10.1016/j.ymgme.2016.05.001
43. Costagliola G, Peroni DG, Consolini R. Beyond infections: new warning signs for inborn errors of immunity in children. *Front Pediatr.* 2022;10:855445. doi:10.3389/fped.2022.855445
44. Yakoboski E, Fuleihan RL, Sullivan KE, Cunningham-Rundles C, Feuille E. Lymphoproliferative Disease in CVID: a Report of Types and Frequencies from a US Patient Registry. *J Clin Immunol.* 2020;40(3):524–530. doi:10.1007/s10875-020-00769-8
45. Maglione PJ. Autoimmune and Lymphoproliferative Complications of Common Variable Immunodeficiency. *Curr Allergy Asthma Rep.* 2016;16(3):19. doi:10.1007/s11882-016-0597-6
46. Peng XP, Caballero-Oteyza A, Grimbacher B. Common variable immunodeficiency: more pathways than roads to Rome. *Annu Rev Pathol.* 2023;18:283–310. doi:10.1146/annurev-pathmechdis-031521-024229
47. Ameratunga R, Allan C, Woon ST. Defining Common Variable Immunodeficiency Disorders in 2020. *Immunol Allergy Clin North Am.* 2020;40(3):403–420. doi:10.1016/j.jiac.2020.03.001
48. Costagliola G, Cappelli S, Consolini R. Autoimmunity in primary immunodeficiency disorders: an updated review on pathogenic and clinical implications. *J Clin Med.* 2021;10(20):4729. doi:10.3390/jcm10204729
49. Park JH, Levinson AI. Granulomatous-lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). *Clin Immunol.* 2010;134(2):97–103. doi:10.1016/j.clim.2009.10.002
50. Matson DR, Yang DT. Autoimmune lymphoproliferative syndrome: an overview. *Arch Pathol Lab Med.* 2020;144(2):245–251. doi:10.5858/arpa.2018-0190-RS
51. Consonni F, Gambineri E, Favre C. Alps FAS, and beyond: from inborn errors of immunity to acquired immunodeficiencies. *Ann Hematol.* 2022;101(3):469–484. doi:10.1007/s00277-022-04761-7
52. Molnár E, Radwan N, Kovács G, et al. Key diagnostic markers for autoimmune lymphoproliferative syndrome with molecular genetic diagnosis. *Blood.* 2020;136(17):1933–1945. doi:10.1182/blood.2020005486
53. López-Nevado M, González-Granado LI, Ruiz-García R, et al. Primary immune regulatory disorders with an autoimmune lymphoproliferative syndrome-like phenotype: immunologic evaluation. *Early Diagnosis Manage Front Immunol.* 2021;12:671755. doi:10.3389/fimmu.2021.671755
54. Cepika AM, Sato Y, Liu JM, Uyeda MJ, Bacchetta R, Roncarolo MG. Tregopathies: monogenic diseases resulting in regulatory T-cell deficiency. *J Allergy Clin Immunol.* 2018;142(6):1679–1695. doi:10.1016/j.jaci.2018.10.026
55. Toskov V, Ehl S. Autoimmune lymphoproliferative immunodeficiencies (ALPID) in childhood: breakdown of immune homeostasis and immune dysregulation. *Mol Cell Pediatr.* 2023;10(1):11. doi:10.1186/s40348-023-00167-1
56. Jamee M, Hosseinzadeh S, Sharifinejad N, et al. Comprehensive comparison between 222 CTLA-4 haploinsufficiency and 212 LRBA deficiency patients: a systematic review. *Clin Exp Immunol.* 2021;205(1):28–43. doi:10.1515/jpem-2020-0277
57. Leiding JW, Vogel TP, Santarlas VGJ, et al. Monogenic early-onset lymphoproliferation and autoimmunity: natural history of STAT3 gain-of-function syndrome. *J Allergy Clin Immunol.* 2023;151(4):1081–1095. doi:10.1016/j.jaci.2022.09.002
58. Delmonte OM, Schuetz C, Notarangelo LD. RAG Deficiency: two Genes, Many Diseases. *J Clin Immunol.* 2018;38(6):646–655. doi:10.1007/s10875-018-0537-4
59. Turvey SE, Durandy A, Fischer A, et al. The CARD11-BCL10-MALT1 (CBM) signalosome complex: stepping into the limelight of human primary immunodeficiency. *J Allergy Clin Immunol.* 2014;134(2):276–284. doi:10.1016/j.jaci.2014.06.015
60. Nunes-Santos CJ, Uzel G, Rosenzweig SD. PI3K pathway defects leading to immunodeficiency and immune dysregulation. *J Allergy Clin Immunol.* 2019;143(5):1676–1687. doi:10.1016/j.jaci.2019.03.017
61. Jamee M, Moniri S, Zaki-Dizaji M, et al. Immunological, and genetic features in patients with activated PI3Kδ Syndrome (APDS): a systematic review. *Clin Rev Allergy Immunol.* 2020;59(3):323–333. doi:10.1007/s12016-019-08738-9
62. Tessarin G, Rossi S, Baronio M, et al. Activated phosphoinositide 3-kinase delta syndrome 1: clinical and immunological data from an Italian cohort of patients. *J Clin Med.* 2020;9(10):3335. doi:10.3390/jcm9103335
63. Delmonte OM, Castagnoli R, Calzoni E, et al. Inborn errors of immunity with immune dysregulation: from bench to bedside. *Front Pediatr.* 2019;7:353. doi:10.3389/fped.2019.00353
64. Sève P, Pacheco Y, Durupt F, et al. Sarcoidosis: a clinical overview from symptoms to diagnosis. *Cells.* 2021;10(4):766. doi:10.3390/cells10040766
65. Kaufman KP, Becker ML. Distinguishing blau syndrome from systemic sarcoidosis. *Curr Allergy Asthma Rep.* 2021;21(2):10. doi:10.1007/s11882-021-00991-3
66. Dispenzieri A, Fajgenbaum DC. Overview of Castleman disease. *Blood.* 2020;135(16):1353–1364. doi:10.1182/blood.2019000931
67. Liu AY, Nabel CS, Finkelman BS, et al. Idiopathic multicentric Castleman's disease: a systematic literature review. *Lancet Haematol.* 2016;3(4):e163–75. doi:10.1016/S2352-3026(16)00006-5
68. Santacruz JC, Mantilla MJ, Rueda I, Pulido S, Rodriguez-Salas G, Londono J. A practical perspective of the hematologic manifestations of systemic lupus erythematosus. *Cureus.* 2022;14(3):e22938. doi:10.7759/cureus.22938
69. Perry AM, Choi SM. Kikuchi-Fujimoto Disease: a Review. *Arch Pathol Lab Med.* 2018;142(11):1341–1346. doi:10.5858/arpa.2018-0219-RA
70. McClain KL, Bigenwald C, Collin M, et al. Histiocytic disorders. *Nat Rev Dis Primers.* 2021;7(1):73. doi:10.1038/s41572-021-00307-9
71. Cheuk W, Bledsoe JR. IgG4-related lymphadenopathy. *Semin Diagn Pathol.* 2024;41(2):108–115. doi:10.1053/j.semmp.2024.01.003
72. Costagliola G, Maiorino G, Consolini R. Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome (PFAPA): a clinical challenge for primary care physicians and rheumatologists. *Front Pediatr.* 2019;7:277. doi:10.3389/fped.2019.00277
73. Wang A, Manthiram K, Dedeoglu F, Licameli GR. Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome: a review. *World J Otorh Head Neck Surg.* 2021;7(3):166–173. doi:10.1016/j.wjorl.2021.05.004
74. Jeyaratnam J, Frenkel J. Management of mevalonate kinase deficiency: a pediatric perspective. *Front Immunol.* 2020;11:1150. doi:10.3389/fimmu.2020.01150
75. Latour S, Fischer A. Signaling pathways involved in the T-cell-mediated immunity against Epstein-Barr virus: lessons from genetic diseases. *Immunol Rev.* 2019;291(1):174–189. doi:10.1111/imr.12791
76. Pachlopnik Schmid J, Canoni D, Moshous D, et al. Clinical similarities and differences of patients with X-linked lymphoproliferative syndrome type 1 (XLP-1/SAP deficiency) versus type 2 (XLP-2/XIAP deficiency). *Blood.* 2011;117(5):1522–1529. doi:10.1182/blood-2010-07-298372

77. Riaz IB, Faridi W, Patnaik MM, Abraham RS. A systematic review on predisposition to lymphoid (B and T cell) Neoplasias in patients with primary immunodeficiencies and immune dysregulatory disorders (Inborn Errors of Immunity). *Front Immunol*. 2019;10:777. doi:10.3389/fimmu.2019.00777
78. Haas OA. Primary Immunodeficiency and Cancer Predisposition Revisited: embedding Two Closely Related Concepts Into an Integrative Conceptual Framework. *Front Immunol*. 2019;9:3136. doi:10.3389/fimmu.2018.03136
79. Taylor AMR, Rothblum-Oviatt C, Ellis NA, et al. Chromosome instability syndromes. *Nat Rev Dis Primers*. 2019;5(1):64. doi:10.1038/s41572-019-0113-0
80. Tiri A, Masetti R, Conti F, et al. Inborn Errors of Immunity and Cancer. *Biology*. 2021;10(4):313. doi:10.3390/biology10040313
81. Cunningham-Rundles C. Common variable immune deficiency: case studies. *Hematology Am Soc Hematol Educ Program*. 2019;2019(1):449–456. doi:10.1182/hematology.2019002062
82. Nishith N, Siddiqui SH, Raja SK R, Agrawal N, Phadke S, Sharma S. Utility of morphologic assessment of bone marrow biopsy in diagnosis of lysosomal storage disorders. *Indian J Pathol Microbiol*. 2023;66(1):91–95. doi:10.4103/ijpm.ijpm_725_21
83. Chen M, Wang J. Gaucher disease: review of the literature. *Arch Pathol Lab Med*. 2008;132(5):851–853. doi:10.5858/2008-132-851-GDROTL
84. Foucher B, Vila L. Bone marrow smear examination in the diagnosis of Niemann-Pick B disease. *Blood*. 2016;128(5):738. doi:10.1182/blood-2016-04-710988
85. Miano M, Madeo A, Cappelli E, et al. Defective FAS-mediated apoptosis and immune dysregulation in gaucher disease. *J Allergy Clin Immunol Pract*. 2020;8(10):3535–3542. doi:10.1016/j.jaip.2020.06.065

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