



REVIEW ARTICLE

Immunodeficiencies: non-infectious manifestations

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Abstract

Objectives: Classical immunodeficiencies are mainly characterized by infectious conditions. In recent years, manifestations related to allergy, inflammation, autoimmunity, lymphoproliferation, and malignancies related to this group of diseases have been described. The text intends to make an update on the non-infectious manifestations of the primary defects of the immune system.

Source of data: Searches were carried out in the PubMed database for review articles published in the last five years, in English, French, or Spanish, using the terms ‘‘allergy,’’ ‘‘inflammation,’’ ‘‘autoimmunity,’’ ‘‘lymphoproliferation,’’ ‘‘cancer,’’ AND ‘‘immunodeficiency’’ or ‘‘primary immunodeficiency’’ or ‘‘inborn errors of immunity’’ NOT ‘‘HIV’’.

Synthesis of data: Non-infectious manifestations characterize the primary defects in which there is dysregulation of the immune system. The most common manifestations of autoimmunity in this group of diseases are autoimmune cytopenias. Exacerbated inflammatory processes, benign lymphoproliferation, and propensity to malignancy of the lymphoreticular system are related to several diseases in this group. Severe manifestations of atopy or food allergy characterize some immunodeficiencies. Disorders of inborn immunity of the autoinflammatory type are characterized by an aseptic inflammatory process in the absence of autoimmunity, with fever and recurrent manifestations in different organs.

Conclusions: Not only infectious conditions should raise the suspicion of immunodeficiencies, but also manifestations of allergy, inflammation, autoimmunity, lymphoproliferation, or cancer, especially if they are recurrent, associated to each other, affecting young patients, or in severe and/or difficult to treat conditions.

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Introduction

Diseases that include primary immune system defects are called primary immunodeficiencies (PIDs). They are mainly characterized by repeated, severe infections that are difficult to treat, requiring the use of intravenous antibiotic therapy and/or present with atypical manifestations, caused by common or opportunistic microbial agents, which are different or always of the same type.¹ These are the classic immunodeficiencies.²

However, the number of diseases with a primary defect of the immune system, which are characterized more by immune dysregulation than deficiency has been increasing and are known as primary immune regulatory disorders (PIRDs).² These diseases have manifestations related to allergy, inflammation, and autoimmunity, with lymphoproliferation or malignancies, which have been described and can be associated with at least 129 diseases distributed in the ten immunodeficiency classification tables.¹ Therefore, a change to the term inborn errors of immunity (IEI) was proposed, to designate this very heterogeneous group consisting of 416 diseases.^{1,3}

Objectives

The aim was to produce an update on the non-infectious manifestations of IEI.

Source of data

A search was performed in PubMed for review articles published in the last five years in English, French, or Spanish using the following terms: “allergy,” “inflammation,” “autoimmunity,” “lymphoproliferation,” “cancer” AND “immunodeficiency” or “primary immunodeficiency” or “inborn errors of immunity” NOT “HIV.”

Results

Several publications have shown that non-infectious manifestations of IEI are common. A study carried out in Slovenia identified non-infectious and non-malignant manifestations in 29% of patients diagnosed with IEI: 22% autoimmunity, 12% lymphoproliferation, 5% autoinflammation, and 4% allergy.⁴ Shortly afterwards, Fisher et al.⁵ published data from the French IEI registry, where they found one or more autoimmune or inflammatory complications in 26.2% of the patients, the most common being autoimmune cytopenias (31.4%) and gastrointestinal manifestations (24.4%). A study with a large number of cases in the registry of the United States Immunodeficiency Network (USIDNET), showed an increased relative risk of 1.42 for cancer in patients with IEI compared to the general population of the same age group, with a relative risk increase of 1.91 in men and similar risk to the general population in women.⁶ Malignancies were found in 8.7% of patients with common variable immunodeficiency.⁷

Non-infectious manifestations may appear in patients with a confirmed diagnosis of IEI or they may be the first

manifestations of the disease, prompting the diagnostic investigation.⁸ They will be presented separately, as follows.

Allergy

In IEI, allergic manifestations most commonly occur in association with infectious, autoimmune, or other manifestations.⁹ However, they can also occur alone, known as primary allergic disorders and manifesting as urticaria, food allergy, asthma, atopic dermatitis, or even just as eosinophilia and increased serum IgE.¹⁰ They may be manifestations of true allergy or only reflect the activation of Th2 mechanisms due to different defects in the immune system pathways. Overall, they are more severe manifestations than in individuals without an IEI, but they are usually clinically similar.¹⁰

Table 1 shows the allergic and associated manifestations in different IEI.

Findings that raise suspicion of a primary allergic disorder in the absence of other associated manifestations, such as infections or autoimmunity, are as follows: very early onset; more severe and/or atypical manifestations and/or associated allergic manifestations; family history of autoimmunity and/or repeated infections, even in the absence of allergy; presence of characteristics such as overall developmental delay, cognitive impairment, joint hypermobility, scoliosis, and others.^{9,10}

Autoimmunity

Approximately a quarter of patients diagnosed with an IEI have one or more manifestations of autoimmunity or inflammation.⁵ In fact, manifestations of autoimmunity can appear in virtually all IEI; however, they are more common in patients with a diagnosis of common variable immunodeficiency and in patients with some cell immunity defect.⁵ Early and/or multiple manifestations of autoimmunity should raise the suspicion of an IEI as a underlying disease, especially if associated with infectious conditions.^{11,12}

The autoimmune diseases most commonly associated with IEI are cytopenias: anemia, thrombocytopenia, neutropenia, and Evans syndrome (anemia and thrombocytopenia). The risk of autoimmune cytopenia is assumed to be approximately 120 times higher in individuals with an IEI than in the general population.⁵ Other manifestations of autoimmunity/inflammation that may be part of the clinical picture of IEI include the following: endocrinopathies, systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, vitiligo, bullous pemphigoid, atrophic gastritis, inflammatory bowel disease, and autoimmune enteropathy.^{13,14} Children diagnosed with an IEI are 80 times more likely to have inflammatory bowel disease and 40 times more likely to have arthritis than the general pediatric population.⁵

There are at least five clinical patterns of autoimmunity in IEI: “ALPS-like” (autoimmune lymphoproliferative syndrome)–autoimmune cytopenias and lymphoproliferation; “CVID-like” (common variable immunodeficiency)–hypogammaglobulinemia, infections, and hematological and solid organ autoimmunity;

Table 1 Allergy manifestations and associated manifestations in different inborn errors of immunity.

Allergy manifestations	Associated manifestations	Inborn errors of immunity (name/gene)
Elevated IgE and eosinophilia	Bacterial skin and pulmonary infections (with pneumatoceles); chronic mucocutaneous candidiasis; altered inflammatory response (cold abscesses); connective tissue abnormalities (hypermotility, scoliosis, retention of primary teeth, fractures, typical facies, aneurysms); non-flexural eczematous dermatitis; exanthema in the neonatal period.	STAT3 defect - Hyper-IgE S.AD ^a (Job S.) Defects in the STAT3 pathway - SNF341, IL6ST, IL6R
Atopy (atopic dermatitis, asthma)/ food allergy/ anaphylaxis	Immune dysregulation; increased IgE and eosinophilia; viral skin infections; combined immunodeficiency (non-severe)	Actinopathies: Wiskott-Aldrich S. and defect in WIP ^b (thrombocytopenia with small platelets); defects in DOCK8, ARPC1B, CARMIL2 Defects in CARD9, CARD11, CARD14, MALT1 PGM3 defect
Severe atopic dermatitis and/or erythroderma / ichthyosis	Increased IgE and eosinophilia; scoliosis; bacterial lung and skin infections; myoclonus and cognitive delay; lymphopenia. Immune dysregulation (enteropathy); bacterial / viral infections; short stature Important eosinophilia; impaired growth. Eosinophilia Lymphoproliferation (hepatosplenomegaly, lymphadenopathy); severe combined immunodeficiency; barrier defects, with major ichthyosis; increased IgE and eosinophilia; bamboo hair; increased metabolic expenditure.	STAT5b LF ^c JAK1 GF ^d Omenn S. Comel-Netherton S. (SPINK5)
Urticaria and anaphylaxis	Dermatitis with skin ulcers; increased IgE; bacterial skin and pulmonary infections; hepatosplenomegaly. Neonatal urticaria; very important eosinophilia; growth alteration. Early and severe hives; erythema and pruritus; anaphylaxis.	Prolidase deficiency STAT5b GF ^d PLAID ^e (evaporative cooling; PLCG2 GF ^d) Familial vibratory urticaria (ADGRE2) Hereditary alpha-tryptasemia (TPSAB1)

Source: Milner, 2020.^{9,10}

^a Autosomal dominant.

^b WAS Interacting Protein.

^c Loss of function.

^d Gain of function.

^e PLCG2-associated antibody deficiency and immune dysregulation.

“IPEX-like” (enteropathy, autoimmune endocrinopathies, eczema, vasculitis); “IBD” (inflammatory bowel disease); and rheumatological diseases—Behçet, lupus, and monogenic juvenile idiopathic arthritis.^{2,15}

Table 2 describes the IEI that most often present with autoimmunity/inflammation and the associated clinical conditions.¹³

Inflammation

Inflammatory conditions related to IEI present as hemophagocytic lymphohistiocytosis (HLH) or as autoimmune inflammatory diseases.

HLH is a severe and often fatal hyperinflammatory syndrome associated with tissue infiltration (bone marrow,

Table 2 Inborn errors of immunity and most commonly related autoimmune and inflammatory manifestations.

Inborn errors of immunity	Associated autoimmune/inflammatory diseases
X-linked agammaglobulinemia	Juvenile idiopathic arthritis, rheumatoid arthritis, inflammatory bowel disease, type I diabetes mellitus, autoimmune cytopenias
Common variable immunodeficiency	Juvenile idiopathic arthritis, rheumatoid arthritis, inflammatory bowel disease, type I diabetes mellitus, autoimmune cytopenias, pernicious anemia, celiac disease, systemic lupus erythematosus, Sjögren syndrome, vitiligo
Selective IgA deficiency	Juvenile idiopathic arthritis, rheumatoid arthritis, inflammatory bowel disease, type I diabetes mellitus, autoimmune cytopenias, celiac disease, systemic lupus erythematosus, Sjögren syndrome, vitiligo
HyperIgM syndrome	Autoimmune hemolytic anemia, immune thrombocytopenic purpura, inflammatory bowel disease, type I diabetes mellitus, discoid lupus
Hyper IgE syndrome	Systemic lupus erythematosus, bullous pemphigoid, rheumatoid arthritis, immune thrombocytopenic purpura, juvenile dermatomyositis
Omenn syndrome	Hashimoto's thyroiditis, inflammatory bowel disease, immune thrombocytopenic purpura
DiGeorge syndrome	Immune thrombocytopenic purpura, autoimmune hemolytic anemia, Hashimoto's thyroiditis, Graves' disease, inflammatory bowel disease, uveitis, juvenile idiopathic arthritis
Wiskott-Aldrich syndrome	Immune neutropenia, immune thrombocytopenic purpura, autoimmune hemolytic anemia, rheumatoid arthritis, juvenile idiopathic arthritis, inflammatory bowel disease
Telangiectasia ataxia	Autoimmune hemolytic anemia, immune thrombocytopenic purpura, Hashimoto's thyroiditis, juvenile idiopathic arthritis
Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)	Autoimmune hypoparathyroidism, autoimmune hepatitis, Hashimoto's thyroiditis, Graves' disease, primary cholangitis, type I diabetes mellitus, vitiligo, psoriasis
Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX)	Autoimmune enteropathy, type I diabetes mellitus, autoimmune cytopenias, Hashimoto's thyroiditis, eczema
LRBA or CTLA4 deficiency	Autoimmune cytopenias, Hashimoto's thyroiditis, inflammatory bowel disease, type I diabetes mellitus, systemic lupus erythematosus, juvenile idiopathic arthritis
Autoimmune lymphoproliferative syndrome (ALPS)	Immune thrombocytopenic purpura, autoimmune hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis
Chronic granulomatous disease	Systemic lupus erythematosus, inflammatory bowel disease, immune thrombocytopenic purpura, type I diabetes mellitus, juvenile idiopathic arthritis, rheumatoid arthritis
Complement system defects	Systemic lupus erythematosus, dermatomyositis, rheumatoid arthritis, juvenile idiopathic arthritis

Adapted from Amaya-Urbe et al., 2019.¹³

liver, ganglia, spleen, skin, and central nervous system) and high production of inflammatory cytokines by activated lymphocytes and macrophages.^{16,17} When related to autoinflammatory, autoimmune diseases, or malignancies, it is often called macrophage activation syndrome.¹⁸

Virtually any IEI in which immune dysregulation mechanisms are involved can evolve with an HLH, whether or not associated with viral infections, particularly Epstein-Barr virus (EBV). However, the defects classically related to this clinical condition are familial hemophagocytic lymphohistiocytosis (FHLH) syndromes with or without hypopigmentation.^{1,19} In both groups, there are cytotoxicity defects and the trigger for HLH may be a viral infection. Among the FHLH syndromes, defects in the PFR1 (perforin) and UNC13D genes are the most common.²⁰ In

hypopigmentation syndromes, Chédiak-Higashi syndrome, Griscelli syndrome type 2, and Hermansky-Pudlak syndrome types 2 and 10, there is partial oculocutaneous albinism, neurological disorders, neutropenia, and/or coagulation disorders.¹

Cytotoxicity is normal or only partially affected in other IEI associated with HLH. IEI with EBV-related lymphoproliferation may also evolve with HLH: X-linked lymphoproliferative syndromes, ITK and CD27 deficiency, and XMEN syndrome (X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia).²¹ Despite T-cell deficiency, combined (non-severe) immunodeficiencies can be complicated with HLH by macrophage activation.²² This mechanism is also responsible for HLH in autoinflammatory diseases, as in the NLRC4 defect,

Table 3 Criteria for the diagnosis of hemophagocytic lymphohistiocytosis, primary or secondary.

Five of the eight criteria below or clinical data with genetic diagnosis of disease associated with hemophagocytic lymphohistiocytosis
1. Fever $\geq 38.5^{\circ}\text{C}$
2. Splenomegaly
3. Cytopenias (at least two of the below)
Hemoglobin $< 9\text{ g/dL}$
Platelets $< 100,000/\text{mL}$
Neutrophils $< 1000/\text{mL}$
4. Hypertriglyceridemia ($> 265\text{ mg/dL}$) and/or hypofibrinogenemia ($< 150\text{ mg/dL}$)
5. Hemophagocytosis identified in bone marrow, spleen, ganglia, liver or other tissues
6. Decreased or absent NK cell activity
7. Ferritin $> 500\text{ ng/mL}$
8. Increase in soluble CD25 ^a ($> 2400\text{ U/mL}$)
Other clinical and laboratory findings that may be associated: meningoencephalic signs and symptoms, adenomegaly, jaundice, edema, exanthema, alterations in liver enzymes, hypoproteinemia, hyponatremia, increased VLDL, and decreased HDL.

VLDL, very low-density lipoprotein; HDL, high-density lipoprotein.

Source: Henter, 2007²³ and Risma, 2019.¹⁷

^a The same as sIL2R α .

the monogenic autoinflammatory disorder characteristically associated with macrophage activation syndrome.^{17,18}

Regarding IEI, the differential diagnosis with sepsis is crucial and, therefore, a high level of suspicion is necessary. What is identified is a condition similar to sepsis, but without the identification of an infectious agent and/or without improvement with antimicrobial use.²¹

Table 3 describes the diagnostic criteria for HLH, based on the HLH-2004 protocol, updated in 2007.^{17,23} It is important to mention that ferritin is usually above $2000\text{ }\mu\text{g/L}$ and that values $> 10,000\text{ }\mu\text{g/L}$ have high diagnostic specificity in children.^{19,21} The only identified variable that is associated with higher mortality in HLH in patients with IEI is hypoalbuminemia. One study found that albumin values $< 3.07\text{ g/dL}$ were associated with a 5.8-fold increase in HLH mortality.²²

The term autoinflammatory diseases (AID) was introduced in the late 1990s, to describe clinical conditions characterized by spontaneous inflammation in the absence of autoimmunity. Currently, it is known that AID constitute innate immunity regulation defects, in which there is hypersecretion of inflammatory cytokines. These diseases are characterized by a recurrent or persistent inflammatory

process, in the absence of an infectious process and absence of autoantibodies or autoreactive T cells.²⁴

In this text, we describe the monogenic AID, which appear in childhood as fever and clinical and laboratory signs of systemic inflammation, different skin rashes, and different patterns of sterile inflammation in other organs, which vary according to the specific autoinflammatory disease. The signs and symptoms are often recurrent and characteristic of each patient, most commonly involving skin and mucosal membranes, digestive tract, musculoskeletal system, and eyes.²⁵

Considering facing recurrent episodes of inflammatory manifestations, with or without fever, with laboratory evidence of altered inflammatory activity, it is important to attempt to identify any infectious agent or search for laboratory evidence of autoimmunity or malignant diseases. After ruling out these causes, the possibility of an AID must be considered, but the definitive diagnosis is only possible through genetic investigation. Aiming to better guide this investigation or to implement treatment in the absence of a genetic diagnosis, it is essential to characterize the clinical phenotype: age at symptom onset, ethnicity of ascendants, habitual triggers of episodes, duration and interval of acute episodes, and details on the signs and symptoms that characterize the condition.^{26,27}

There have been many proposed classifications and they generally use clinical data or pathophysiological mechanisms. Table 4 shows a very useful classification, based on clinical data: fever patterns, type of skin lesion, and type of organ-specific inflammation.²⁸

Due to their frequency among the AID, Table 5 shows the new classification criteria proposed by the Eurofever project for hereditary recurrent fevers.²⁹ The criteria proposed by Eurofever for periodic fever, aphthosis, pharyngitis, and adenitis (PFAPA) include at least seven among the following eight items: presence of pharyngotonsillitis; duration of episodes between three to six days; cervical adenitis; periodicity; with no diarrhea, chest pain, skin rash, or arthritis.²⁹

Benign lymphoproliferation

Lymphoid proliferation with adenomegaly and/or splenomegaly occurs in many IEI and is closely related to immune dysregulation mechanisms with or without viral infections, particularly EBV. In addition there is the possibility that it is caused by bacteria or intracellular fungi infections, which will not be discussed here.

In association with immune dysregulation, due to apoptosis or cytotoxicity defects, lymphoproliferation is usually associated with autoimmune manifestations, mainly autoimmune cytopenias, endocrinopathies or enteropathy, or is associated with hyperinflammatory conditions, such as hemophagocytic lymphohistiocytosis.¹

Despite the overlapping of mechanisms related to immune dysregulation with or without viral infections, one or another basic lymphoproliferation mechanism predominates in some IEI. Common variable immunodeficiency, the most common symptomatic IEI, corresponds to the defect most often related to lymphoproliferation caused by immune dysregulation, with others being autoimmune

Table 4 Autoinflammatory diseases classified according to fever pattern and/or type of skin lesion and associated inflammatory manifestations.

Clinical manifestations	Autoinflammatory diseases
Group 1 Recurrent/episodic fever with or without skin rash Short-duration fever Longer-lasting fever	Familial Mediterranean fever, Hyper IgD TRAPS
Group 2 Neutrophilic urticaria Short-duration recurrent fever Persistent inflammation with episodes of exacerbation	FACS Muckle-Wells Syndrome, NOMID/CINCA
Group 3 Pustular exanthema and episodic fever Pyogenic disease with sterile osteomyelitis Pyogenic disease with sterile pyogenic arthritis Pustular disorder with a picture similar to Behçet Pustular disorder with psoriasis-like condition Pustular disorder with inflammatory bowel disease Pyogenic disease with varied mechanisms	DIRA, Majeed Syndrome PAPA HA20 DITRA, CAMPS, AMPS IL10, IL10R, NISBD1 PAAND, PFIT
Group 4 Vasculopathy and panniculitis/lipodystrophy Mediated by type I interferon Partially dependent on TNF	CANDLE, PRAAS ORAS
Group 5 Vasculopathy with or without vasculitis and livedo No significant demyelination and with interstitial pulmonary disease With central nervous system demyelinating disease With spondyloenchondrodysplasia With stroke	SAVI AGS. Pseudo TORCH SPENCD DADA2
Group 6 Cutaneous granulomatosis Without immunodeficiency With immunodeficiency	Blau syndrome PLAID, APLAID, NDAS
Group 7 Macrophage activation syndrome With NK and TCD8 defects and immunodeficiency	NLRC4, LACC1 FLH, Chédiak-Higashi, Griscelli, Hermansky-Pudlak
Group 8 Others	Cherubism, SIFD, AISLE, NLRP12, TNFRSF11A, NAIAD

TRAPS, TNF receptor-associated periodic syndrome; FACS, familial cold autoinflammatory syndrome; NOMID/CINCA, neonatal-onset multisystem inflammatory disease/ chronic infantile neurological cutaneous and articular syndrome; DIRA, deficiency of the interleukin-1 receptor antagonist; PAPA, pyogenic arthritis, pyoderma gangrenosum and acne syndrome; HA20, haploinsufficiency of A20; DITRA, deficiency of the IL-36 receptor antagonist; CAMPS, caspase activation and recruitment domains (CARD)14-mediated psoriasis; AMPS, AP1S3-mediated psoriasis; NISBD1, neonatal inflammatory skin and bowel disease 1; PAAND, pyrin-associated autoinflammation with neutrophilic dermatosis; PFIT, periodic fever, immunodeficiency, and thrombocytopenia; CANDLE, chronic atypical neutrophilic dermatoses with lipodystrophy and elevated temperature syndrome; PRAAS, proteasome-associated autoinflammatory syndromes; ORAS, otulin-related autoinflammatory syndrome; SAVI, stimulator of IFN genes (STING)-associated vasculopathy with onset in infancy; AGS, Aicardi-Goutières syndrome; SPENCD, spondyloenchondrodysplasia with immune dysregulation; DADA2, deficiency of adenosine deaminase 2; PLAID, cold-induced urticaria and or granulomatous rash; APLAID, PLC-γ2 associated antibody deficiency and immune dysregulation; NDAS, nuclear factor (NF)-κB essential modulator (NEMO) deleted exon 5 autoinflammatory syndrome– X-linked; LACC1, LACC1-mediated monogenic Still disease; FLH, familial hemophagocytic lymphohistiocytosis; SIFD, congenital sideroblastic anemia, B-cell immunodeficiency, periodic fevers, and developmental delay; AISLE, autoinflammatory syndrome-associated with lymphedema; NAIAD, NLRP1-associated autoinflammation with arthritis and dyskeratosis.

Adapted from Goldbach-Mansky & de Jesus, 2019.²⁸

Table 5 Criteria for the classification of recurrent hereditary fevers.

CAPS ^a	FFM ^b	TRAPS ^c	MKD ^d
Presence of mutation in NLRP3 and at least one of the following: <ul style="list-style-type: none"> ● urticarial rash ● red eye (conjunctivitis, episcleritis, uveitis) ● sensorineural hearing loss 	Presence of MEFV mutation and at least one of the following: <ul style="list-style-type: none"> ● Duration of episodes between 1–3 days ● Arthritis ● Chest pain ● Abdominal pain 	Presence of mutation in TNFRSF1A and at least one of the following: <ul style="list-style-type: none"> ● Duration of episodes ≥ 7 days ● Myalgia ● Migratory skin rash ● Periorbital edema ● Affected family members 	Presence of MKV mutation and at least one of the following: <ul style="list-style-type: none"> ● Gastrointestinal symptoms ● Cervical adenitis ● Foot-and-mouth disease
OR	OR	OR	OR
Absence of mutation in NLRP3 and at least 2 of the following: <ul style="list-style-type: none"> ● urticarial rash ● red eye (conjunctivitis, episcleritis, uveitis) ● sensorineural hearing loss 	Absence of mutation in MEFV and at least 2 of the following: <ul style="list-style-type: none"> ● Duration of episodes between 1–3 days ● Arthritis ● Chest pain ● Abdominal pain 	Absence of mutation in TNFRSF1A and at least 2 of the following: <ul style="list-style-type: none"> ● Duration of episodes ≥ 7 days ● Myalgia ● Migratory skin rash ● Periorbital edema ● Affected family members 	

Adapted from Gattorno, 2019.²⁹

^a Periodic syndromes associated with cryopyrin.

^b Familial Mediterranean fever.

^c Periodic fever syndrome associated with the tumor necrosis factor receptor.

^d Mevalonate kinase deficiency or hyper IgD syndrome.

Table 6 Inborn errors of immunity according to the lymphoproliferation mechanism and associated clinical and laboratory manifestations.

Lymphoproliferation mechanism	Other manifestations	Inborn error of immunity
Immune dysregulation	Combined T and B cells defect, eosinophilia, erythroderma	Omenn S.
	Combined T and B cells defect, progressive CD4 lymphopenia, normal B cells, normal to low immunoglobulins	ITK deficiency ^a
	Antibody defect, decreased IgG and IgA and/or IgM, sinopulmonary infections, autoimmune cytopenias	Common variable immunodeficiency
	Antibody defect, decreased IgG and IgA with normal or increased IgM, bacterial infections, autoimmunity	APDS ^{a,b}
	Antibody defect, low or normal immunoglobulins and B lymphocytes, hematological and thyroid autoimmunity	NFKB1 deficiency ^a
Related to EBV (Epstein-Barr virus)	Treg cell defects, hematological or solid organ autoimmunity, enteropathy	CD25 and CD122 ^a deficiency STAT3GF ^c
	Normal or high T cells, normal or reduced memory B cells, normal or reduced immunoglobulins, dysgammaglobulinemia ^d	X-linked lymphoproliferative syndromes (by mutations in SAP or XIAP), deficiencies in CD27, CD70 ^e , CTP51, CD137, RASGRP1, RLTPR, PRKCD ^e and XMEN

Source: Tangye, 2020.¹

^a May be related to EBV.

^b p110 δ activation syndrome.

^c Gain of function.

^d Antibodies in normal quantity, but with altered function.

^e May be related to autoimmunity.

Table 7 Inborn errors of immunity most often related to the development of cancer, type of defect involved, and associated malignancies.

Types of defects	Inborn errors of immunity	Associated malignancies
Disorders with DNA break	Ataxia telangiectasia Bloom syndrome Nijmegen syndrome DNA ligase IV mutations	Lymphomas and leukemias, breast cancer Lymphomas, acute leukemias and carcinomas Lymphomas, leukemias, CNS tumor Lymphomas, leukemias
Antibody defects	Common variable immunodeficiency	Non-Hodgkin's lymphoma, gastric, thyroid or skin cancer. Lymphomas Gastrointestinal tract tumor Lymphomas and carcinomas
Non-severe combined defects (T and B)	Activated p110δ syndrome (APDS) Selective IgA deficiency Artemis syndrome, ADA defects, ZAP 70, RAG1 and Coronin 1A (non-severe phenotype) Wiskott-Aldrich syndrome	Lymphomas, acute lymphocytic leukemia, Kaposi's sarcoma, myelodysplastic syndrome Lymphomas Lymphomas, leukemias, epithelial tumors, and others Lymphomas and leukemias, thyroid carcinoma, neuroblastoma, hepatoblastoma, Wilms' tumor. Liver, pancreas, and biliary pathway carcinomas Hodgkin's and non-Hodgkin's lymphomas
	Hair cartilage hypoplasia DOCK8 mutation	Lymphomas, leukemias, epithelial tumors, and others
	DiGeorge syndrome	Lymphomas and leukemias, thyroid carcinoma, neuroblastoma, hepatoblastoma, Wilms' tumor.
	Hyper IgM syndrome	Liver, pancreas, and biliary pathway carcinomas Hodgkin's and non-Hodgkin's lymphomas
Immune dysregulation	Autoimmune lymphoproliferative syndrome (ALPS) Susceptibility to EBV: X-linked lymphoproliferative syndrome, deficiencies of ITK, CD70, CD27, RASGRP1, CTPS1, CD137, MAGT1, CARMIL2, PRKCD Familial hemophagocytic lymphohistiocytosis associated with hypopigmentation IL10R deficiency Chronic mucocutaneous candidiasis	EBV ^a -associated lymphomas ^a Lymphomas Lymphomas Squamous cell tumors of the oral cavity and esophagus Myelodysplastic syndrome, acute myeloid leukemia, chronic myelomonocytic leukemia, EBV ^a and HPV ^b tumors Myelodysplastic syndrome, acute myeloid leukemia, squamous cell carcinomas of the head and neck, breast cancer Leukemias, myelodysplastic syndrome, squamous cell carcinomas of the head and neck, lung tumors, gastrointestinal tract, and liver Myelodysplastic syndrome and acute myeloid leukemia Myelodysplastic syndrome and acute myeloid and acute lymphocytic leukemia Acute or chronic myeloid leukemias Skin cancer (HPV) ^p Skin cancer
	GATA2 deficiency	Myelodysplastic syndrome, acute myeloid leukemia, chronic myelomonocytic leukemia, EBV ^a and HPV ^b tumors
	Fanconi anemia	Myelodysplastic syndrome, acute myeloid leukemia, squamous cell carcinomas of the head and neck, breast cancer
	Congenital dyskeratosis	Leukemias, myelodysplastic syndrome, squamous cell carcinomas of the head and neck, lung tumors, gastrointestinal tract, and liver
Bone marrow defects	Mirage syndrome and ataxia-pancytopenia syndrome Congenital neutropenia	Myelodysplastic syndrome and acute myeloid leukemia Myelodysplastic syndrome and acute myeloid and acute lymphocytic leukemia
	Shwachman-Diamond syndrome Verruciform epidermodysplasia WHIM ^c	Acute or chronic myeloid leukemias Skin cancer (HPV) ^p Skin cancer
Defects in innate immunity		

Source: Mortaz, 2016; Haas, 2019; Kebudi, 2019; Riaz, 2019; Renzi, 2020; Rezaei, 2020; Khalil, 2020. 33-38

^a Epstein-Barr virus.

^b Human papilloma virus.

^c Syndrome with warts, hypogammaglobulinemia and myelokathexis.

lymphoproliferative syndrome (ALPS) and activated p110 δ syndrome (APDS). In the latter, persistent EBV and/or cytomegalovirus (CMV) viremia is common.¹

Defects with EBV-related lymphoproliferation, usually without autoimmunity manifestations, are the X-linked lymphoproliferative syndromes (caused by mutations in SAP or XIAP), and CD27, CD70, CTPS1, CD137, RASGRP1, RLTPR, PRKCD, and XMEN deficiencies.¹

When treating a patient diagnosed with an IEI with lymphoproliferation, considering the possibility of infections and the associated malignancy potential, surveillance through ganglion biopsies, ideally by excision, with phenotyping and clonality studies, in addition to investigating infectious agents, are essential.³⁰

The IEI that are most commonly related to lymphoproliferation are shown in Table 6.¹

Malignancies

Malignancies occur more frequently and earlier in life in patients with IEI and are the second cause of death in children and adults with this diagnosis, after infectious conditions.^{31,32} The increased risk of cancer in patients with IEI identified by the USIDNET study⁶ refers mainly to lymphomas, leukemias, and stomach cancer.

One of the immune system's functions is to identify and eradicate tumor cells, known as immune surveillance. Many immune system pathways that protect against infections also act in this surveillance.³³ However, the risk of the most common malignancies in the general population of men and women (colon, breast, lung, and prostate) is similar in individuals with IEI.⁶ This means that the immune surveillance system probably plays a limited role in the control of these tumors.³³

Considering the limited spectrum of malignancies associated with IEI, the small proportion of patients with IEI among patients with malignant diseases, and the relatively small number of IEI related to cancer, other mechanisms besides immunological surveillance have been implicated.³¹ Other mechanisms proposed for the association between IEI and malignancies include the following: chronic tissue inflammation, DNA repair defects, telomere maintenance defects, myeloid cell development defects, infections, as well as apoptosis, cytotoxicity or metabolic defects.³¹ Many malignancies in patients with IEI are related to viral diseases, most commonly EBV, which appears to be related to the development of 30% to 60% of lymphoma cases.³⁴ However, other viruses may be involved: the human herpes virus (HHV 6 and 8), the human papillomavirus (HPV), the human T-cell lymphotropic virus (HTLV), and CMV.^{35,36}

The most common malignancies identified in patients with IEI are non-Hodgkin's lymphoma, mainly the B-cell type, leukemias, and gastric cancer. They affect patients with antibody defects, especially with common variable immunodeficiency, due to their high frequency among the IEI.^{33,36} However, the IEI with the highest risk of evolution to a malignant disease is ataxia-telangiectasia, in which there is a defect in DNA repair.³⁴ Regarding solid tumors, the one most commonly described in patients with IEI is the gastric carcinoma, particularly in common variable immunodeficiency.³⁴

IEI patients tend to have malignancies earlier in life than the general population. One study shows that lymphomas appear between 7 months and 76 years, with a mean age of 12 years.³⁶ The chance of a child with an IEI to develop cancer varies between 5% and 25%, and the type of cancer depends on the type of immune defect.³⁷

Table 7 shows the IEIs most commonly related to the development of cancer and the malignancies most often associated with them.^{33,38}

Specific treatment

The treatment of non-infectious manifestations of IEI is, at least initially, similar to that performed for these same manifestations when they occur outside the context of IEI. The use of immunosuppressive medications requires extra care, as there is a risk of increasing the chance of infections.³⁹

However, in more severe cases and/or poorly responsive to these therapeutic resources, the diagnosis of a monogenic disease implies the indication of drugs directed to the immune system pathways involved in the specific defect and/or hematopoietic stem-cell transplantation (HSCT).^{2,39} One example is the very early-onset inflammatory bowel disease related to a monogenic defect: when severe and/or unresponsive to immunosuppressants or immunobiological agents, HSCT is indicated and is curative. Gene therapy is a prospect for the perhaps not-too-distant future.³⁹

Conclusions

Not only should repeated, severe, difficult-to-treat, and/or opportunistic microorganism infections raise suspicion of IEI, but also manifestations of allergy, inflammation, autoimmunity, lymphoproliferation, or cancer, particularly if they are recurrent, associated with each other, affect young patients, present as severe conditions, and/or are difficult to treat.

The initial treatment of non-infectious manifestations associated with IEI differs little from their treatment when they are not related to IEI. However, when an IEI is diagnosed, specific medications may be indicated and, in severe cases, hematopoietic stem cell transplantation appears as a therapeutic option.

Conflicts of interest

The authors declare no conflicts of interest.

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