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Primary immunodeficiencies and lymphoma: a systematic review of literature

Mathilde Herber[a], Philippe Mertz[b], Yannick Dieudonné[a], Blandine Guffroy[c,d], Sophie Jung[e,f], Vincent Gies[a,f,g], Anne-Sophie Korganow[a,d,f] and Aurélien Guffroy[a,d,f]

[a]Department of Clinical Immunology and Internal Medicine, National Reference Center for Systemic Autoimmune Diseases (RESO), Tertiary Center for Primary Immunodeficiency, Strasbourg University Hospital, Strasbourg, France; [b]Department of Rheumatology, National Reference Center for Systemic Autoimmune Diseases (RESO), Strasbourg University Hospital, Strasbourg, France; [c]Department of Onco-Hematology, Strasbourg University Hospital, Strasbourg, France; [d]UFR Médecine, Université de Strasbourg, Strasbourg, France; [e]Faculty of Dentistry, Strasbourg University - Reference Center for Oral Rare Diseases (O-Rares), Strasbourg University Hospital, Strasbourg, France; [f]INSERM UMR - S1109, Faculté de Médecine, Fédération Hospitalo-Universitaire OMICARE, Fédération de Médecine Translationnelle de Strasbourg (FMTS), Strasbourg University, Strasbourg, France; [g]UFR Sciences Pharmaceutiques, Université de Strasbourg, Strasbourg, France

ABSTRACT

The management of lymphoma in patients with primary immunodeficiency (PID) is challenging because of its poor prognosis and complex therapeutic approaches. We conducted a systematic literature review of case-reports, case-series, and cohorts indexed in MEDLINE reporting the association of lymphoma and PID. One hundred and eighty-two articles were selected out of 787. We identified 386 cases. Median age at diagnosis of PID and lymphoma was 9.5 and 12 years old, respectively. T-cell deficiencies were the main PIDs associated with lymphoma (57%). The most prevalent lymphoma was diffuse large B-cell lymphoma (33.5%). Epstein–Barr Virus-driven lymphomas were mostly observed in innate immunodeficiencies (when reported). Complete response to treatment was observed in 65.8% of the cases. Death occurred in 38.2%. Few allogenic stem cell transplantations were performed (29 cases). Our detailed analysis of the literature provides a landscape of lymphoma's occurrence in PID. Devoted studies in specific sub-groups of patients at risk are needed to develop dedicated protocols.

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Lymphoma; lymphoproliferative disorders; primary immunodeficiency; PID; EBV

Introduction

Primary immunodeficiencies (PIDs) are a heterogeneous and increasing group of more than 350 genetic diseases affecting the development and/or the function of various components of the innate and adaptive immune system [1]. Pathophysiology of PIDs is now better characterized thanks to high throughput genomic investigations allowed by next-generation sequencing [2].

Life expectancy in PIDs is reduced due not only to enhanced susceptibility to infections, but also to non-infectious complications such as autoimmunity (AI) or malignancy. Indeed, the risk of lymphoma is increased up to 10-fold in PID patients compared to age- and sex-matched subjects [3] and the risk of developing cancer in childhood ranges from 4% to 25% [4] with up of two-thirds of hematological malignancies [5,6]. In adults, lymphoma occurs in 3–8% of common variable immunodeficiency (CVID) patients [7–10] and represents 35% of all tumors [11].

Numerous mechanisms of lymphomagenesis could play a role such as molecular signaling abnormalities, lack of immuno-surveillance, and persistent antigen stimulation by pathogens or by transforming viruses [12]. In this way, Epstein–Barr Virus (EBV) is involved in 30 to 60% of lymphoma cases associated with PIDs [13]. However, lymphoma can also reveal an underlying PID. For example, in CVID, lymphoma develops before the onset of PID in 22% of cases and precedes the diagnosis up to several months [11]. The therapeutic management of PIDs is further complicated by the association with lymphoma, and conversely an underlying PID in a patient with lymphoma may have short- or long-term consequences on the management of lymphoma. Some patients remain deeply immunosuppressed for months or even years after

CONTACT Aurélien Guffroy aurelien.guffroy@chru-strasbourg.fr Department of Clinical Immunology and Internal Medicine, National Reference Center for Systemic Autoimmune Diseases, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

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chemotherapies and require a specific management (antibioprophylaxis, immunoglobulin substitution). Patients with PID and lymphoma have significant morbidity and mortality risks and consequently a challenging management in a daily-basis.

Herein, we present a systematic literature review of PID-associated lymphomas and report the main characteristics of these patients, including the type of PID, precise lymphoma histology, treatment, and outcomes. This detailed analysis of individual cases is completed by a compilation of PIDs cohorts describing an association with lymphoma.

Materials and methods

Definitions

PIDs classification

PIDs were defined according to the 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies [1]. According to this classification, we generate four main categories as follows (Supplementary material, Table S1):

- Predominant B cell immunodeficiencies
- T cell immunodeficiencies
- Innate immunity deficiencies
- Unclassified immune deficiency

To describe and study the prevalence of the different PID subtypes, we used the data available in the ESID Registry Database (last update 2014, available at www.esid.org).

Lymphomas classification

Lymphomas were classified according to the WHO 2016 classification [14]. In some cases ($n = 61/386$), the collected data on lymphoma characteristics did not allow a reclassification according to the WHO 2016 classification. In those cases, the lymphoma type was reported as defined in the source article and listed in 'lymphoma unclassified' category.

To describe and study the prevalence of the different lymphoma subtypes, we used the data available on two sources: (1) the US Lymphoid Malignancy Statistics [15] (2016); (2) the French Lymphopath Network [16] (2017).

Data source

We performed a systematic review of the literature using case-reports and case-series indexed in MEDLINE in order to assess the association of lymphoma and PIDs (until 30 December 2018). The following MeSH search equation was used: (('Lymphoma'[Majr]) AND (('Immunologic Deficiency Syndromes'[Majr]) OR ('primary immunodeficiency')) NOT ('HIV Infections'[Majr]) NOT ('Deltaretrovirus Infections'[Majr]) (Not animals). Because this equation did not capture all PIDs, especially for recently genetically described ones, we performed a second line of research including the exact denomination of each PID of the IUIS 2017 classification adding the term (('Lymphoma'[Majr])).

Article selection

All articles reporting one or more original cases (with available individual data) of lymphoma occurring in a context of PID were independently selected by two different authors (M.H. and P.M.). The first level of articles selection was based on title and abstract. Secondary lymphomas (to HIV, HTLV1, or immunosuppressive treatments), other types of hematological diseases or cancer (i.e. solid tumors) were excluded. At this step, Kappa correlation coefficient was 0.82. Remaining articles were independently analyzed by M.H. and P.M. Unavailable full articles were excluded (lack of data, no archive available). Secondary lymphoma occurring after the treatment of a first lymphoma or after allogeneic hematopoietic stem cell transplantation (HSCT) was also excluded from the analysis to avoid confusion bias. At this step, remaining discrepancies ($n = 21/787$) between M.H. and P.M. were resolved through consensus with the participation of one supervisor author (A.G).

Cohorts were defined as articles reporting two or more cases without individual description of the cases.

Data assessment

For each selected article, demographic, clinical, and paraclinical data, as well as data on prognosis, treatment, and follow-up regarding both PID and lymphoma were collected according to a pre-defined data-collection chart.

Statistical analysis

Extracted data are presented as median (25–75th percentile interquartile range, IQR) or number (percentage). Survival analyses were performed by using the Kaplan-Meier nonparametric model to estimate the time to event and analyzed by the log rank test. Threshold for statistical significance was set to a p value of <0.05 in all analysis. Analyses were performed

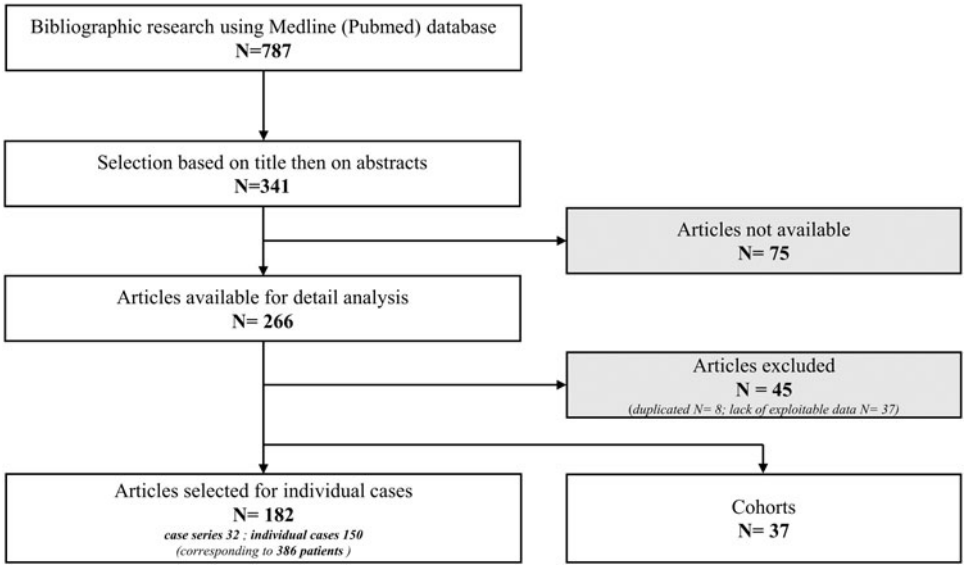


Figure 1. Flow chart of the study.

using software JMP Version 13 (SAS Institute Inc., Cary, NC, USA) and GraphPad Prism version 7 (GraphPad software Inc, San Diego, CA, USA).

Results

Description of individual cases or case-series groups and cohort groups

Our bibliographic research identified 787 articles in Medline. Three hundred and forty-one articles were selected through title and abstract. Among them, 182 articles (32 cases series and 150 individual case reports) corresponding to 386 individual patients with lymphoma, fulfilled our selection criteria (Figure 1). The median age at diagnosis of PID was 9.5 years and median age at diagnosis of lymphoma was 12 years. Sex ratio (F/M) was 4/6 (40.2% of women) (Table 1).

In addition to individual cases, we analyzed the results of 37 cohorts describing the incidence of lymphoma in a given PID category. Six cohorts reported B-cells deficiencies, representing 31 patients with lymphoma among 280 PID patients (median age between 5 and 35.9 years), 10 cohorts focused on T-cells immunodeficiencies with 79 patients that developed lymphoma among 258 patients (median age between 1 and 12.5 years), and 21 cohorts concerned innate immune deficiencies with more than 196 patients with lymphoma among 790 reported patients (median age between 0 and 24.5 years) (Table 2).

Altogether, published literature of individual cases, case-series or cohorts confirmed that lymphoma is frequently associated with PID and can affect young patients but also adults depending of the PID category.

Types of PIDs presenting with lymphoma

In registries, 'predominantly antibody disorders' (i.e. B-cell PIDs) represents the most prevalent group with 56.66% of reported PID cases in ESID registry. 'Predominantly T-cells deficiencies' (i.e. T-cells deficiencies) are less common PIDs with a prevalence of 7.46%. 'Innate immune deficiencies' represent 14.6% of PIDs cases in registries regardless of the etiology (including complement deficiencies, phagocytic disorders, auto-inflammatory and immune dysregulation syndromes, and defects of innate components).

In our case series, T-cell deficiencies are over-represented among the described cases of PID patients with lymphoma (57% of cases) and Ataxia Telangiectasia (AT) is the most frequent reported PID (112 cases, 29%). B-cell immunodeficiencies account for 29.6% of the patients with CVID representing 78.3% of B-cells PIDs. Finally, 14% of described patients with lymphoma have innate immune deficiency and in 0.5% of the cases immune deficiency is categorized as unclassified (Table 1, Figure 2 and Table S2).

Considering associated manifestations in PID patients developing lymphoma, a benign lymphoproliferation (LP) was reported prior to the diagnosis of lymphoma in 15.7% of the cases. Deficiencies of innate immunity (26.7%) were the most frequent PID type associated with benign LP (e.g. 80% in autoimmune lymphoproliferative syndrome—ALPS). AI was reported in 8.9% of the cases and was particularly

Table 1. Characteristics of patients with lymphoma and PID.

Type of PID	Numbers of patients % *N*	Age of diagnosis (PID) % (median; IQR) *N*	Age of diagnosis (lymphoma) % (median; IQR) *N*	Female % *N*	Familial cases (PIDs) % *N*	Known mutations % *N*	Benign LP % *N*	AI % *N*	Infections (opportunistic, severe, or recurrent) % *N*	Treatments ATBX % *N*	Treatments Ig substitution % *N*	Treatments Allogeneic HSCT % *N*
Overview												
Total	386	8.5 (9; 30)	12 (6; 22.2)	40.2 (129/321)	17 31/182	30.1 (77/255)	18.7 (32/171)	8.8 (34/384)	74.5 (137/184)	10.1 (34/336)	41.6 (72/173)	15.8 (29/183)
B-Cells PIDs												
Total	28.2	28 (8.5; 43.5)	31 (12; 46.7)	50.5	20.3	7.5	25.4	33.9	77.8	10.3	74.5	0
	109	71/ 109	102/109	52/106	14/69	5/67	15/59	20/59	42/54	11/106	38/51	0/56
B-cell CVIDs	78.3	30 (10.5; 44)	35 (16; 50.3)	54.9	17.3	5.4	29.8	36.2	88.1	12.3	80.5	0
	83	60/83	81/83	45/82	9/52	3/55	14/47	17/47	37/42	10/81	33/41	0/46
Other B-cell deficiencies	23.8	12 (2; 34.75)	14 (6; 21)	29.1	29.4	16.7	8.3	25	41.7	4	50	0
	26	12/ 26	21/26	7/24	5/17	2/12	1/12	3/12	5/12	1/25	5/10	0/10
T-Cells PIDs												
Total	57	5.5 (0; 15.5)	10 (6; 17)	40.5	35.3	30	7.9	7	71.8	7.3	23.9	19
	220	88/220	197/220	64/158	41/116	39/130	9/114	7/100	74/103	15/205	23/96	20/105
SCID	7.2	0 (0; 1)	1 (0; 3.5)	53.3	35.7	60	9.1	16.7	91.7	0	37.5	33.3
	17	11/17	16/17	8/15	5/14	9/15	1/11	2/12	11/12	0/17	3/8	4/12
CID	1.4	5.5 (5; 6)	11 (6.5; 11.5)	100	100	100	50	50	100	33.3	0	50
	3	2/3	3/3	3/3	2/2	3/3	1/2	1/2	2/2	1/3	0/2	1/2
Others T-cells PIDs	90.9	6 (2 ;15,5)	12 (16; 17)	37.8	34	24.1	6.9	4.6	68.5	7.6	23.2	16.5
	200	75/ 200	177/200	53/140	34/100	27/112	7/101	4/86	61/89	14/185	20/86	15/91
Innate deficiencies	14.2	7 (2.75; 15.5)	6 (3; 14)	21.8	51.1	54.5	26.7	30.4	87.5	32	46.1	29
	55	28/55	53/55	12/55	23/45	30/55	8/30	7/23	21/27	8/25	12/26	9/31
Unclassified deficiencies	0.5	4,25 (2.5; 6)	2.5 (2.5; 2.5)	50	100	100	0	0	100	0	0	0
	2	2/2	2/2	1/2	2/2	2/2	0/1	0/2	1/1	0/1	0/1	0/1

PID: primary immunodeficiency; AI: Autoimmunity; ATBX: Antibiophrophylaxis; LP: Lymphoproliferation; Ig: Immunoglobulin; N: Number; HSCT: Haematological Stem Cell Transplantation. All percentage are given in function of available data for each parameter. The number of available data is given in the second line of each category.

Table 2. Characteristics of patients with lymphoma and PIDs in literature cohorts.

PID type	Reference	Gene	Number of cases of lymphoma *N/N* patients	Age (median; IQR)	Type of lymphoma %B/%T	EBV-associated lymphoma %	LP %	Infections %	AI %	Treatments %ATBX/%IVIg/%HSCT	Mortality related to lymphoma %
B-cell deficiencies	Tanyildiz_2016	CVID	2/2	5	100/0	ND	ND	ND	ND	ND/ND/50	0
		IgA deficiency	1/1	12	100/0	ND	ND	ND	ND	ND/ND/ND	100
	Egg_2018	CTLA4	10/184	35.9	100/0	70	0.5	5,4	Yes but MD	ND/30/20	50
	Coulter_2017	PIK3CD	7/53	17.2	13/0	42.8	75	98	42	62/87/9	42.8
	Elkaim_2016	PIK3R1	9/36	18	28/0	11.1	89	100	17%	61/89/8	ND
	Crequer_2012	RHOH	1/2	ND	100/0	0	ND	ND	ND	ND/ND/ND	0
	Schipp_2018	STK4	1/2	10	100/0	0	50	ND	50	ND/ND/ND	0
T-cell deficiencies	Taylor_1992	AT	5/60	6	40/40	ND	0	ND	ND	ND/ND/ND	ND
	Kutluk_2000	AT	6/6	8	100/0	ND	ND	ND	ND	ND/ND/ND	ND
	Suarez_2014	AT	50/69	12.5	76/8	38	ND	ND	ND	ND/ND/ND	32
	Tanyildiz_2016	AT	7/7	7	85.7/14.3	ND	ND		ND	ND/ND/ND	33.3
	Nagai_2013	LYST	1/15	1	ND	ND	ND	67	ND	ND/ND//40	0
	De Vos_2006	PMS2	3/13	ND	33.3/66.7	ND	ND	ND	ND	ND/ND/ND	66.7
	Kruger_2007	PMS2	1/6	10	ND	ND	ND	ND	ND	ND/ND/ND	0
	Kruger_2008	PMS2	1/6	ND	0/100	0	ND	ND	ND	ND/ND/ND	0
	De Vos_2016	PMS2	2/13	6.5	50/50	ND	ND	ND	ND	ND/ND/ND	100
	Farmer_2019	RAG (RAG1/RAG2)	3/63	ND	66/33	50	ND	ND	100	ND/ND/ND/ND	ND
Innate deficiencies	Salzer_2012	CD27	3//8	ND	66.7/33.3	66.7	37.5	ND	0	ND/25/25	33.3
	Latour_2018	CD27	6/18	1–22	92.3/7.7	66.7	66.7	33.3	33.3	ND/ND/ 22.2	23
		CD70	4/6	1–5	100/0	83.3	83.3	50	0	ND/ND/ 16.7	0
		CORO1A	4/9	0.5–7	100/0	55.6	55.5	100	0	ND/ND/ 22.2	44.4
		CTPS1	2/12	0–5	100/0	41.7	41.7	83.3	0	ND/ND/ 75	75
		MAGT1	5/11	3–45	100/0	63.6	63.6	81.8	27.2	ND/ND/ 18.2	27.2
		ITK	9/13	2.5–18	100/0	100	100	84.6	23	ND/ND/ 30.1	53.9
		RASGRP1	4/6	5–12	100/0	66.7	66.7	100	50	ND/ND/ 33.3	50
		SH2D1A	20–30/>100	0.5–40	95/5	25–30	ND	15	3–4	ND/ND/10–40	20–50
		XIAP	ND/>100	0.5–41	ND	ND	ND	ND	1–40	ND/ND/ 10–30	5–30
	Purtilo_1982	EBV-LPS	35/100	ND	2.8/ND	100	ND	ND	ND	ND/ND/ND	5.7
	Neven_2011	TNFRSF6	7/90	24.5	100/0	14.3	99	ND	61	ND/ND/ND	ND
	Price_2014	FAS	18/150	18	94.4/0	44.4	97%	ND	ND	ND/ND/ND	57.1
	Straus_2001	FAS	10/130	ND	80/20	ND	ND	ND	ND	ND/ND/ND	ND
	Neven_2013	IL-10R	5/5	5.8	100/0	0	0	ND	ND	ND/ND/ND	80
	Ghosh_2014	ITK	6/9	2.3	100/0	ND	44.4	ND	33.3	ND/ND/22.2	100
	Cipe_2015	ITK deficiency	2/2	4,25	100/0	100	100	Yes but MD	0	ND/ND/ND	100
	Bienemann_2015	ITK	7/7	5	ND	100	100	ND	ND	ND/ND/ND	71.4
	Li_2014	MAGT1	4/7	14.5	100/0	100	ND	Yes but MD	ND	ND/ND/ND	ND
	Somekh_2018	RASGRP1	6/9	ND	ND	100	100	Yes but MD	55.5	ND/ND/ND	0
	Winter_2017	RASGRP1	2/2	5.5	100/0	100	ND	Yes but MD	ND	ND/ND/50	50
	Alkhairy_2015	TNFRSF7/CD27	6/17	ND	83.3/16.7	ND	35.3	47	ND	ND/58.8/17.6	50
	Sumazaki_2001	SH2D1A	3/10	4.1	100/0	100	ND	ND	ND	ND/ND/20	ND
	Morra_2001	SH2DA1	2/8	9.6	100/0	ND	ND	Yes but MD	ND	ND/ND/ND	0
	Booth_2010	SH2D1A	19/91	ND	94.7/5.3	ND	ND	ND	ND	ND/ND/ND	ND
	Schmid_2011	SH2DA1	10/33	15 (2–40)	90/10	60	ND	ND	ND	ND/30.3/6.1	20
	Marsh_2014	SH2D1A	8/16	4	100/0	ND	ND	ND	ND	ND/ND/ND	0
		SH2DA1	4/17	9.5	100/0	0	ND	ND	ND	ND/ND/ND	25
	Tanyildiz_2016	ALPS	1/1	14	100/0	100	ND	ND	ND	ND/ND/ND	0
		WAS	1/1	4	100/0	ND	ND	ND	ND	ND/ND/ND	0
		ITK deficiency	1/1	4	0/100	ND	ND	ND	ND	ND/ND/ND	100
		EBV-LPS	2/2	11.5	100/0	ND	ND	ND	ND	ND/ND/ND	50

PID: primary immunodeficiency; LP: lymphoproliferation; AI: autoimmunity; *N*: number; IQR: inter-quartile range; ATBX: antibioprophylaxie; Ig: immunoglobulin; HSCT: Hematological Stem Cell Transplantation; ND: no data; MD: Missing Data.

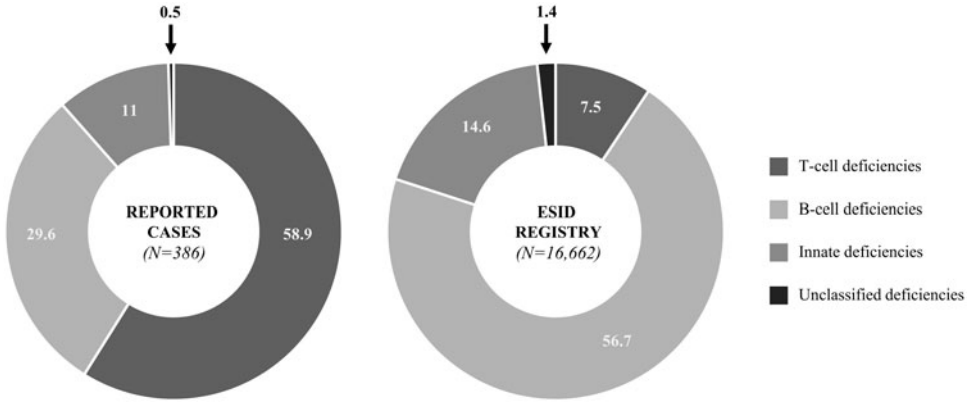


Figure 2. Distribution of PIDs with lymphoma, compared to global prevalence of PIDs according to ESID registry (2014). Frequency of PIDs subtypes among patients with PIDs and lymphoma described in the literature as compared to global distribution of PIDs according to ESID registry (esid.org).

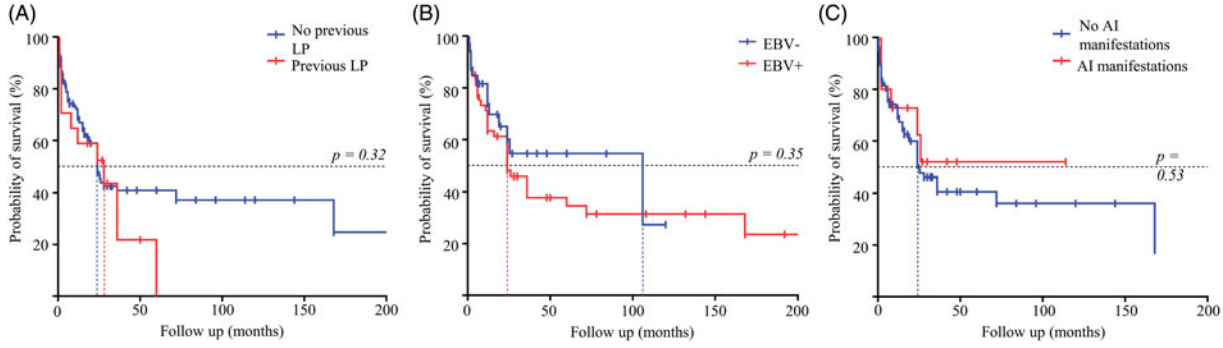


Figure 3. Survival analysis of patients with PIDs as a function of the occurrence of (A) previous benign LP, (B) EBV driven lymphoma, (C) autoimmune manifestations.

prevalent in patients with B-cell PIDs, especially CVID (36.2%), as well as in patients with PIDs affecting innate immunity (30.4%). Comparison with the French national PIDs registry (CEREDIH; [17]) is given in Table S3. Severe, recurrent, or opportunistic infections were reported in 75% of the cases during the course of PID and lymphoma, in particular in innate immune deficiencies (87.5%) (Table 1).

Altogether, these data are in accordance with the fact that PID patients with complications (LP, AI, I) represent a high-risk group in terms of morbidity and mortality. Indeed, they cumulate several risks including malignancy. However, due to lack of data in many cases, Kaplan–Meier analysis did not reach statistical significance between survival probability and occurrence of previous benign LP ($p = 0.32$; Figure 3(A)), EBV-driven lymphoma ($p = 0.35$; Figure 3(B)), or autoimmune manifestations ($p = 0.53$; Figure 3(C)).

Lymphomas occurring in PID

We observe two peaks of incidence of lymphoma associated to PIDs. The first one occurs during childhood at about 7.5 years of age (4–11) and the second occurs later in life, during the third decade, at approximately 32 years (20–47). The diagnosis of PID precedes the diagnosis of lymphoma in 89.8% of cases with a diagnosis-delay ranging from 2 to 5 years (Table S2 and Figure S1).

Figure 4 represents the repartition of lymphomas associated with PIDs, and in parallel, the global prevalence according to the US Lymphoid Malignancy Statistics (2016) and the registry from the French Lymphopath Network (2017), as defined by the WHO 2016 classification of lymphoma. In PIDs, the most frequently reported lymphoma types were diffuse large B-cell lymphoma (DLBCL) (33.5%), Burkitt lymphoma (7.1%), followed by follicular lymphoma (mostly in late-onset lymphomas group), and mixed cellularity classical Hodgkin lymphoma (mostly in early-onset group) both representing 6.8% of the cases. Lymphomas were diffuse (stage III/IV) in most cases (67.2%), regardless of the patient's age in children and adult-onset lymphomas (respectively, 64.8% in children and 68.2% in adults). EBV was not systematically researched with a lack of data for many biopsies (EBV testing reported in 37.3% of cases). Considering the 76 EBV-driven lymphomas among 144 patients with

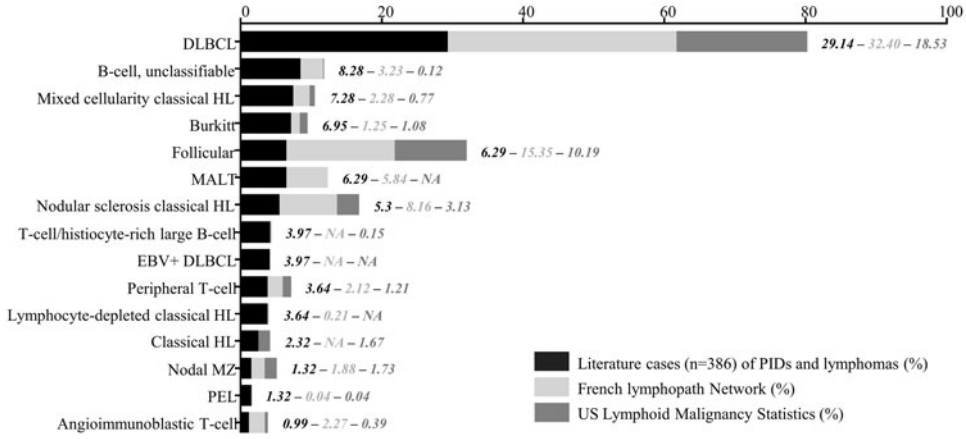


Figure 4. Lymphoma distribution amongst PIDs types. Frequencies of lymphoma in PIDs classified within the WHO 2016 classification (386 cases) compared to the French Lymphopath registry and US registry.

available data (52.8%), the most represented types were DLBCL (38.2%), follicular lymphoma (13.2%), and mixed cellularity classical HL (10.5%). EBV-driven lymphomas were more frequently associated with innate (78.7%) and T-cell (46.2%) deficiencies and mostly in young patients (Table 2).

Management and outcome of lymphomas in PID

Complete response to treatment was observed in 65.8% of the cases, with 78.4% in innate immune deficiencies, followed by B-cell deficiencies (66.7%) and T-cell deficiencies (62.3%). Death was directly caused by lymphoma progression or its treatment in 38.2% of the cases, especially in severe combined immunodeficiency (SCID). Infectious complications were significant as they represented 32.3% of the death causes (second death cause in this literature-series after lymphoma-related causes).

Thirty-eight cases reported the use of reduced chemotherapy dosages ranging from 20 to 75% compared to the standard of care: 17 patients survived, 9 died (7 of lymphoma progression, 1 of other PID complication, 1 other cause) and for 12 patients, no data concerning survival were available. In 10 cases, an adjustment of the therapeutic protocol has been made due to the underlying PID, mainly with rituximab used in monotherapy: 5 patients survived, 4 died (with 2 deaths linked to lymphoma progression), and for 1 patient, no data were available on the outcome. Few allogeneic stem cell transplantations were performed ($n = 29$ cases), with 7 deaths (3 infections, 2 lymphoma progression, 1 other, 1 ND).

Antibiotic prophylaxis was reported in 10.1% of the cases. Trimethoprim–sulfamethoxazole, azithromycin, acyclovir, and fluconazole were mainly used. 42% of the patients (72/173) received intravenous immunoglobulin (IVIg), especially in CVID (74.5%).

These data highlight the diversity of the treatments used for lymphoma's management when it occurs concomitantly with PID. There is undoubtedly a need of dedicated studies to improve and coordinate the practices.

Cohorts analysis

In addition to individual cases or case-series, we report the data from 37 cohorts describing lymphoma in a given PID category (Table 2).

PIDs with susceptibility to EBV and lymphoma

Latour and Winter [18] and Tangye et al. [19] recently reviewed cases of lymphomas in EBV-associated PIDs: SH2D1A deficiency with a risk of 25–30% to develop lymphoma, ITK deficiency (9 patients with lymphoma/13), MAGT1 deficiency (5/11), CORO1A deficiency (4/9), CD27 deficiency (6/18), CTPS1 deficiency (2/12), RASGRP1 deficiency (4/6), and CD70 deficiency (4/6). B-cell lymphomas were predominant, especially DLBCL and Hodgkin lymphomas. EBV viremia was important, ranging from 35 to 100% depending on the gene that is mutated, leading to EBV-lymphoma in all ITK deficient patients compared to 25–83.3% in other genetic defects. LP before lymphoma was reported in all described mutations and varied from 41.7% in CTPS1 deficiency to 100% in ITK deficiency. Infections were observed in all patients, especially in CORO1A and RASGRP1 deficiencies. Autoimmune manifestations were predominant in RASGPR1 (50%) and XIAP (until 40%) deficient patients. HSCT was performed in all cases. Lymphoma-related mortality varied from 0% (CD70 deficiency) to 75% (CTPS1 deficiency).

Six other authors reported several cases of lymphomas associated to SH2D1A deficiency (Brandau et al. [20] in 1999 (4 lymphomas/17), Morra et al. [21,22] (2/8), and Sumazaki et al. [23] (3/10) in 2001, Booth et al. [24] (19/91), Schmid et al. [25] (10/33) in 2011, and Marsh et al. [26] in 2014 (8/16)). B-cell lymphomas were largely predominant (94.7–100% of cases), with the implication of EBV reported in 25–100% of the cases. HSCT was performed in 10–40% of the cases. Lymphomas related mortality was high in these series, ranging from 20 to 50%.

Somekh et al. [27] and Winter et al. [28] recently described six lymphomas in nine patients with RASGRP1 deficiency. In two patients, B-cell lymphomas were linked to EBV. Infections were frequent and autoimmune manifestations occurred in about 50% of the cases.

Salzer et al. [29] and Alkhairy et al. [30] respectively described three cases of lymphoma in 8 patients and 6 lymphomas in 17 patients affected by CD27 deficiency, with two-thirds of B-cell and one-third of T-cell lymphomas. 66.7% of them were associated with EBV. Infections occurred in half of the patients (47%) and no AI was reported. HSCT was performed, respectively, in 17.6 and 25% of the cases with a mortality rate of 33.3%.

Ghosh et al. [31] reported 6 lymphomas in 9 ITK deficient patients (100% of B-cell lymphomas). HSCT was performed in 22.2% of the patients with 100% mortality. Finally, Li et al. [32] reviewed 4 B-cell lymphomas in 7 patients with MAGT1 defects, all associated with EBV.

Altogether, these data highlight that the enhanced susceptibility to EBV, which is frequently observed in PIDs, leads to a high rate of hematological malignancies. HSCT with reduced intensity regiment should therefore be considered as a potential preventive therapy. In some cases of EBV-induced LP associated with these PIDs, rituximab is used efficiently and allows remission.

Activation of PI3K/AKT/mTOR/S6K pathway and lymphoma

Coulter et al. [33] and Elkaim et al. [34] reviewed cases of activated PI3 kinase delta syndrome, i.e. *PIK3CD* and *PIK3R1* gain of function (GOF) mutations. Seven lymphomas were described in 53 *PIK3CD* patients and 9 lymphomas in 36 cases of *PIK3R1* GOF mutations. Only B-cell lymphomas were observed, and they were associated to EBV infection in 42.8% of the cases for *PIK3CD* mutations and in 11.1% of the cases for *PIK3R1* GOF mutations. Those patients were rarely treated by HSCT (9% and 8% in *PIK3CD* and *PIK3R1* GOF, respectively). Lymphoma-related death occurred in 42.8% of *PIK3CD* patients (no data available for *PIK3R1*).

Egg et al. [35] recently described a cohort of 184 patients with *CTLA4* haplo-insufficiency. Ten B-cell lymphomas were reviewed (70% were associated with EBV), with very few infections (5.4%), and a lymphoma-related mortality estimated at 50%. IVIg and HSCT were respectively used in 30% and 20% of the cases.

Defect of apoptosis (FAS/FASL pathway) and lymphoma

Three cohorts of ALPS patients with *FASL* and *TNFRSF6* mutations were included in the analysis: Straus et al. [36] (10 lymphomas/130 patients), Price et al. [37] (18/150), and Neven et al. [38] (7/90). They described a predominance of B-cell lymphomas (80–100%), but the latter were not systematically linked to EBV (14.3–44.4%). Almost all patients presented with previous LP, and autoimmune manifestations were reported in 61% of the cases. One review described 57.1% of mortality related to lymphoma. HSCT procedure was not reported.

CVID Cohorts and lymphoma:

Similarly to AI [39,40], LP is a severity marker in CVID. Cunningham-Rundles and Bodian [9] described some years ago an increased risk of lymphoma associated to CVID that was estimated between 1.4 and 7%. They were mainly extranodal and B-cell lymphomas were the most common types. Out of 22 B-cell lymphomas that developed over a period of 25 years in their cohort of CVID subjects, five were MALT lymphomas. The treatment relied on chemotherapy. No death or infections were reported. In 2008, Oksenhendler et al. [10] described lymphomas in 16/252 patients (6.3%) in the DEFI French national study. Among the European group, Wehr and al. [41] reported 26.2% cases of lymphadenopathy and 40.5% cases of lymphoproliferative disease, without lymphoma, in the EUROclass trial (303 patients). This European cohort demonstrated that lymphadenopathies are significantly associated with splenomegaly and granulomatous disease.

Gathmann and al. [11] described 71 cases of lymphoma out of 203 tumors identified from 2,212 patients in ESID database. Splenomegaly and lymphomas occurred before CVID diagnosis in 22% and 11% of the cases, respectively. Odnoletkova et al. [42] recently described a lymphoma rate of 3.8% diagnosed in 2700 patients from 23 countries (ESID registry data).

Mortality increased with lymphoma (HR 5.48 (2.36; 12.71), $p < 0.0001$) and the prevalence of lymphoma as well as of solid cancers are, respectively, 32.5 and 2.4-fold increased compared to the prevalence rate in the general population.

Other cohorts of PIDs associated with lymphoma

Three AT cohorts (Taylor [43] in 1992, Kutluk et al. [44] in 2000, and Suarez et al. [45] in 2015) reported the same susceptibility to lymphoma that was already observed in individual cases series with a predominance of B-cell lymphoma.

Several other PIDs cohorts listed in Table 2 reported a link with lymphomagenesis (PMS2 deficiency, RAG partial defects).

Discussion

Both PIDs and lymphoma are highly heterogeneous in their causes, classifications, and clinical presentations. As they are also rare diseases, each case is complex and rather unique. Thus, it is of great importance to have a specific and comprehensive literature overview of the other cases to adapt investigations and therapies.

From the physician point of view, it is important to consider that a precise genetic defect is only reported in 20% of the cases (77 out of 386; Table S4). It is also crucial to keep in mind the importance of the age of onset of lymphoma as well as the relative over-representation of T-cells PIDs in childhood-onset lymphoma and of B-cells PIDs (especially CVID) in adulthood-onset lymphoma. In this way, CVID is probably underestimated in our review of cases or case-series, as it is one of the most common causes of PID (1/25,000) and as several cohorts reported a prevalence of lymphoma of about 5%.

The predisposition to lymphoproliferative syndrome of immunocompromised patients can have multiple etiologies that are still not fully understood and may vary from one PID to another. Association with EBV is relatively frequent in some PIDs, but unfortunately it seems to be not systematically tested either in the blood or in histological analysis. Nonetheless, the low proportion of EBV-induced lymphomas in a large amount of other PIDs suggests other causes of lymphomagenesis. One of them is T-cell lymphopenia and NK cells defects, as these cell types are involved in immunosurveillance and elimination of abnormal cells [28,46]. This phenomenon is similar to the lymphomagenesis situation that is encountered in HIV patients [47,48]. In AT and NBS, cell cycle control is compromised, resulting in hypersensitivity to DNA damaging agents (radiotherapy, chemotherapy), and leading to increased susceptibility to malignancies. Lymphoma immunosurveillance, chronic LP following B- and T-cell activation, chronic antigenic stimulation resulting from insufficient antigen elimination, as well as defective apoptosis processes can be combined and favor lymphomagenesis. In CVID, the link between LP (especially splenomegaly) and lymphoma development is reported but remains controversial [11]. Indeed, it is very challenging to evaluate if the risk of lymphoma is increased by a prior history of LP and our study did not reach statistical significance on this point.

Patients with PID are mainly affected with B-cells lymphoma, from extra-nodal origin and of diffuse stages at diagnosis. Burkitt lymphoma is over-represented and it is one of the main types of lymphoma associated with HIV induced-lymphopenia and with EBV chronic infection. In our analysis however, no precise etiology stands out.

Lymphoma appears to be the first manifestation of PID in about 10% of the detailed cases, but this is probably underestimated. These observations highlight the need to explore 'extra-hematologic' features in child or adult populations presenting with lymphoma. Potential red flags should be kept in mind such as family history of PIDs or infections, LP or AI, particularly in young patients diagnosed with lymphomas.

The prognosis of patients with both lymphoma and PID is poor in comparison to immunocompetent individuals affected by similar malignancies. Indeed, one of the main reasons of this discrepancy is the higher complication rate (mostly infections). Myeloablative HSCT regiments remain usually the best option to cure aggressive lymphomas, but this procedure is associated with high morbidity and mortality in PID patients [49]. HSCT with reduced-intensity conditioning was shown to be more effective in several disorders with improved post-HSCT survival [50]. In some identified PIDs, allogeneic transplantation should be considered in accordance to underlying pathophysiology and oncogenesis mechanisms (EBV susceptibility, DNA repair defects). Gene-editing procedures provided the proof of concept that gene therapy can be considered to cure PIDs, especially in patients without HLA-matched stem cell donors in whom toxicity of allogeneic procedures is high.

This systematic literature review confirms the increased risk of lymphoma that is associated to several types of PIDs and provided a current description of PIDs-associated lymphomas. It highlights the need

of international collaborations on these pathologies and their treatments, considering their prognosis, as well as the lack of consensus on therapeutic regiments, HSCT, or other targeted therapies.

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ORCID

Vincent Gies http://orcid.org/0000-0002-8658-8604
Aurélien Guffroy http://orcid.org/0000-0003-0615-5305

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

[1] Picard C, Bobby Gaspar H, Al-Herz W, et al. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018;38(1):96–128.
[2] Seleman M, Hoyos-Bachiloglu R, Geha RS, et al. Uses of next-generation sequencing technologies for the diagnosis of primary immunodeficiencies. Front Immunol. 2017;8:847.
[3] Mayor PC, Eng KH, Singel KL, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the United States Immune Deficiency Network Registry. J Allergy Clin Immunol. 2018;141(3):1028–1035.
[4] Filipovich AH, Mathur A, Kamat D, et al. Primary immunodeficiencies: genetic risk factors for lymphoma. Cancer Res. 52(19 Suppl):5465s–5467s.
[5] Salavoura K, Kolialexi A, Tsangaris G, et al. Development of cancer in patients with primary immunodeficiencies. Anticancer Res. 2008;28:1263–1269.
[6] Leechawengwongs E, Shearer WT. Lymphoma complicating primary immunodeficiency syndromes. Curr Opin Hematol. 2012;19(4):305–312.
[7] Chapel H, Lucas M, Lee M, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood. 2008;112(2):277–286.
[8] Resnick ES, Moshier EL, Godbold JH, et al. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood. 2012;119(7):1650–1657.
[9] Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34–48.
[10] Oksenhendler E, Gérard L, Fieschi C, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis. 2008;46(10):1547–1554.
[11] Gathmann B, Mahlaoui N, Gérard L, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol. 2014;134(1):116.e11–126.e11.
[12] Suarez F. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. Blood. 2006;107(8):3034–3044.
[13] Shapiro RS. Malignancies in the setting of primary immunodeficiency: implications for hematologists/oncologists. Am J Hematol. 2011;86(1):48–55.
[14] Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–2390.
[15] Teras LR, DeSantis CE, Cerhan JR, et al. 2016 US lymphoid malignancy statistics by World Health Organization subtypes: 2016 US Lymphoid Malignancy Statistics by World Health Organization Subtypes. CA: Cancer J Clin. 2016;66:443–459.
[16] Laurent C, Baron M, Amara N, et al. Impact of expert pathologic review of lymphoma diagnosis: study of patients from the French lymphopath network. J Clin Oncol. 2017;35(18):2008–2017.
[17] Fischer A, Provot J, Jais J-P, et al. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immun. 2017;140(5):1388–1393.e8.
[18] Latour S, Winter S. Inherited immunodeficiencies with high predisposition to Epstein–Barr virus-driven lymphoproliferative diseases. Front Immunol. 2018;9:1103.
[19] Tangye SG, Palendira U, Edwards E. Human immunity against EBV—lessons from the clinic. J Exp Med. 2017;214(2):269–283.
[20] Brandau O, Schuster V, Weiss M, et al. Epstein–Barr virus-negative boys with non-Hodgkin lymphoma are mutated in the Sh2D1A gene, as are patients with X-linked lymphoproliferative disease (XLP). Hum Mol Genet. 1999;8(13):2407–2413.
[21] Morra M, Howie D, Grande MS, et al. X-linked lymphoproliferative disease: a progressive immunodeficiency. Annu Rev Immunol. 2001;19(1):657–682.
[22] Morra M, Simarro-Grande M, Martin M, et al. Characterization of SH2D1A missense mutations identified in X-linked lymphoproliferative disease patients. J Biol Chem. 2001;276(39):36809–36816.
[23] Sumazaki R, Kanegane H, Osaki M, et al. SH2D1A mutations in Japanese males with severe Epstein-Barr virus-associated illnesses. Blood. 2001;98(4):1268–1270.
[24] Booth C, Gilmour KC, Veys P, et al. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a

multicenter study on the manifestations, management and outcome of the disease. Blood. 2011;117(1): 53–62.

[25] Schmid JP, Canioni 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.

[26] Marsh RA, Bleesing JJ, Chandrakasan S, et al. Reduced-intensity conditioning hematopoietic cell transplantation is an effective treatment for patients with SLAM-associated protein deficiency/X-linked lymphoproliferative disease type 1. Biol Blood Marrow Transpl. 2014;20(10):1641–1645.

[27] Somekh I, Marquardt B, Liu Y, et al. Novel mutations in RASGRP1 are associated with immunodeficiency, immune dysregulation, and EBV-induced lymphoma. J Clin Immunol. 2018;38(6):699–710.

[28] Winter S, Martin E, Boutboul D, et al. Loss of RASGRP1 in humans impairs T-cell expansion leading to Epstein–Barr virus susceptibility. EMBO Mol Med. 2018;10(2):188–199.

[29] Salzer E, Daschkey S, Choo S, et al. Combined immunodeficiency with life-threatening EBV-associated lymphoproliferative disorder in patients lacking functional CD27. Haematologica. 2013;98(3):473–478.

[30] Alkhairy OK, Perez-Becker R, Driessen GJ, et al. Novel mutations in TNFRSF7/CD27: clinical, immunologic, and genetic characterization of human CD27 deficiency. J Allergy Clin Immunol. 2015;136(3): 703–712.e10.

[31] Ghosh S, Bienemann K, Boztug K, et al. Interleukin-2-inducible T-cell kinase (ITK) deficiency—clinical and molecular aspects. J Clin Immunol. 2014;34(8): 892–899.

[32] Li F-Y, Chaigne-Delalande B, Su H, et al. XMEN disease: a new primary immunodeficiency affecting Mg2+ regulation of immunity against Epstein-Barr virus. Blood. 2014;123(14):2148–2152.

[33] Coulter TI, Chandra A, Bacon CM, et al. Clinical spectrum and features of activated PI3-kinase delta syndrome: a large patient cohort study. J Allergy Clin Immunol. 2016;139(2):597.e4–606.e4.

[34] Elkaim E, Neven B, Bruneau J, et al. Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase δ syndrome 2: a cohort study. J Allergy Clin Immunol. 2016;138(1):210–218.e9.

[35] Egg D, Schwab C, Gabrysch A, et al. Increased risk for malignancies in 131 affected CTLA4 mutation carriers. Front Immunol. 2018;9:2012.

[36] Straus SE, Jaffe ES, Puck JM, et al. The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. Blood. 2001; 98(1):194–200.

[37] Price S, Shaw PA, Seitz A, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. Blood. 2014;123(13): 1989–1999.

[38] Neven B, Magerus-Chatinet A, Florkin B, et al. A survey of 90 patients with autoimmune lymphoproliferative syndrome related to TNFRSF6 mutation. Blood. 2011;118(18):4798–4807.

[39] Guffroy A, Mourot-Cottet R, Gérard L, et al. Neutropenia in patients with common variable immunodeficiency: a rare event associated with severe outcome. J Clin Immunol. 2017;37(7):715–726.

[40] Boileau J, Mouillot G, Gérard L, et al. Autoimmunity in common variable immunodeficiency: Correlation with lymphocyte phenotype in the French DEFI study. J Autoimmun. 2011;36(1):25–32.

[41] Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood. 2008;111(1):77–85.

[42] Odnoletkova I, Kindle G, Quinti I, et al. The burden of common variable immunodeficiency disorders: a retrospective analysis of the European Society for Immunodeficiency (ESID) registry data. Orphanet J Rare Dis. 2018;13:201.

[43] Taylor A. Ataxia telangiectasia genes and predisposition to leukaemia, lymphoma and breast cancer. Br J Cancer. 1992;66(1):5–9.

[44] Kutluk MT, Yalcin B, Büyükpamukçu M. Ataxia telangiectasia and Hodgkin disease. Med Pediatr Oncol. 2000;35(5):509.

[45] Suarez F, Mahlaoui N, Canioni D, et al. Incidence, presentation, and prognosis of malignancies in ataxia-telangiectasia: a report from the French National Registry of Primary Immune Deficiencies. J Clin Oncol. 2015;33(2):202–208.

[46] Verhoeven D, Stoppelenburg AJ, Meyer-Wentrup F, et al. Increased risk of hematologic malignancies in primary immunodeficiency disorders: opportunities for immunotherapy. Clin Immunol. 2018;190:22–31.

[47] Koebel CM, Vermi W, Swann JB, et al. Adaptive immunity maintains occult cancer in an equilibrium state. Nature. 2007;450(7171):903–907.

[48] Taylor JG, Liapis K, Gribben JG. The role of the tumor microenvironment in HIV-associated lymphomas. Biomarkers Med. 2015;9(5):473–482.

[49] Gennery AR, Slatter MA, Grandin L, et al. Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? J Allergy Clin Immunol. 2010;126(3):602.e1-11–610.e1-11.

[50] Fox TA, Chakraverty R, Burns S, et al. Successful outcome following allogeneic hematopoietic stem cell transplantation in adults with primary immunodeficiency. Blood. 2018;131(8):917–931.