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Lymphoid malignancy in common variable immunodeficiency in a single-center cohort

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Abstract

One of the complications of common variable immunodeficiency (CVID) is the development of lymphoid malignancy. In this retrospective, single-center study of 647 CVID subjects followed over 4 decades, we present immunologic and clinical phenotypes, pathology, treatment, and outcomes of 45 patients (15 males and 30 females, 7%) who developed 49 lymphoid malignancies. The mean age at CVID diagnosis was 42.6 years) and at lymphoma diagnosis was 48.8 years. Of the 41 with known follow up, 29 (70%) have died, 27 of these due to this diagnosis. Twelve are alive, in remission or have achieved cure; four others were alive at last encounter. Some patients had a history of only recurrent infections (36.3%); others had autoimmunity (33%), enteropathy (20%), and/or granulomatous disease (11%). Six had previously been treated for another cancer. This report also includes 6 additional living CVID patients who had been diagnosed with NHL; 4 were given treatment for this. However, on pathology review, the initial diagnosis was reversed, as the findings were more consistent with a benign lymphoproliferative process. This study outlines the high incidence of lymphoma in this single CVID cohort, and some of the diagnostic challenges presented due to immune dysregulation characteristic of this immune defect.

Keywords

common variable immune deficiency; genetics; lymphoid hyperplasia; non hodgkin lymphoma

1 | INTRODUCTION

The most common primary immunodeficiency diseases are inborn errors of immunity leading to antibody deficiency.[1,2] The clinical spectrum of antibody deficiencies is broad and patients are often characterized by recurrent or severe infections, as well as non-

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AUTHOR CONTRIBUTIONS

TS and CC-R contributed data collection, analysis, wrote the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

infectious complications such as autoimmunity, inflammatory lung and/or gastrointestinal disease, or malignancy.[3–8] Common variable immunodeficiency (CVID) is the most prevalent of the symptomatic primary immunodeficiencies and has a stronger association with non-infectious complications as compared to other antibody deficiencies such as IgG deficiency or X-linked agammaglobulinemia.[9–13] While immunoglobulin replacement (Ig) therapy limits infections in almost all patients who lack specific antibodies, the non-infectious complications of CVID are often non-responsive to this form of treatment and have become the major source of morbidity and mortality in CVID.[11,12,14] The associated complications consist of not only a number of organ-specific autoimmune and/or inflammatory manifestations but also include generalized benign lymphoproliferation of the lymph nodes, spleen, and other tissue sites such as the lungs.[15–17]

One of the more difficult complications in CVID are malignancies, especially non-Hodgkin lymphoma (NHL), commonly B cell in type, which markedly reduces survival.[11,18–21] The actual prevalence of lymphomas in CVID is unknown but estimates have been made from patient registries and single-center studies. An early estimate of prevalence from the European Society for Immunodeficiencies (ESID) Registry was based on 3 cases in this cohort of 344 subjects (0.9%).[12] More recently, also from the same Registry, 2.5% had lymphoma.[22] This was similar to the US Immunodeficiency Network (USIDNET) Registry, which was 2.9%.[20] Studies from single centers have ranged widely from 1.3% to 9.1%[11,23–26] (Table 1).

It also remains unclear if NHL is more likely to arise in subjects who have a history of autoimmune or inflammatory complications, granulomatous disease, or in those subjects with long-standing lymphoproliferation. As adenopathy, splenomegaly and lymphoid infiltrations, especially in the lungs and gastrointestinal tract, are common in CVID, dissecting benign and malignant forms of lymphoid proliferation can be challenging. Here, we describe the 49 lymphoid malignancies which occurred in 45 subjects in a cohort of 647 CVID subjects (7.0%) who were referred to one New York City medical center practice. We present the immunologic and clinical phenotypes, pathologic features, genetic studies, as well as individual treatments and outcomes of these subjects. In the same CVID cohort, 6 additional CVID subjects had also been diagnosed with NHL; however, upon expert review of pathologic material at the National Cancer Institute (NCI), these diagnoses were revised to other forms of benign lymphoproliferation.

2 | METHODS

2.1 | Subjects

Twelve of these CVID subjects were seen in the Immune Deficiency Clinic at Memorial Sloan-Kettering Cancer Center (1974–1986). After transfer of this practice, those who were alive, and subsequently 33 other CVID subjects who had or later developed lymphoma, were seen at the Mount Sinai Medical Center (1986 through the present.) The diagnosis of CVID was made by standard criteria including: 4 years of age or older, reduced serum IgG, IgA, and/or IgM by at least 2 SDs below the mean for age, poor, or absent antibody production to protein and carbohydrate-based vaccines and exclusion of other causes of hypogammaglobulinemia.[27] Serum immune globulin were recorded at the baseline

levels at the diagnosis of CVID. All subjects diagnosed with lymphoid cancer within 2 years of the CVID diagnosis were also excluded in order to diminish the possibility that pre-existing lymphoma or its treatment led to the immune defect observed. The treatment of lymphomas was recorded from chart information. Whole exome, whole genome, and targeted sequencing to seek immune deficiency genes was performed in 17 of the more recently diagnosed cases, using standard methods.[28]

2.2 | Diagnosis of lymphoid malignancy

The diagnosis of lymphoma for the first 12 patients (until 1986), was based on pathologic examination of tissues at Memorial Sloan Kettering Cancer Center. For 33 other subjects seen at the Mount Sinai Medical Center, pathologic examination was made at this hospital. However, where available, the original diagnostic material in 25 of these cases, was also submitted for expert pathology review to the Laboratory of Pathology, Hematopathology Section, at the National Cancer Institute in Bethesda, Maryland. Studies of histological features and immunophenotyping were performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections according to routine procedures. Immunohistochemical stains were performed according to routine procedures and select stains were used on a case by case basis. Epstein-Barr encoding region (*EBER*) in situ hybridization was performed on sections as previously described.[29] Fluorescence in situ hybridization (FISH) analysis was performed on bone marrow aspirate and lymph node specimens according to standard protocols. At the time of tissue examination. Conventional molecular (PCR for Ig gene rearrangement) were performed when possible and all cytogenetic reports were reviewed.

2.3 | Statistics

To calculate the mean ages and standard deviations of diagnosis of CVID, age at death and at lymphoma diagnosis and to compare immune globulin IgM levels of subjects with lymphoma to other subjects in this cohort (Mann Whitney test), we used GraphPad Prism software.

3 | RESULTS

3.1 | Demographics and immunologic parameters

The overall cohort included 647 CVID patients (288 males and 359 females) referred for their immune deficiency over a 45-year period. Of this group, 45/647 (7.0%) of these previously diagnosed CVID patients were subsequently diagnosed with a lymphoid malignancy, 15 males and 30 females. The mean age at CVID diagnosis was 42.6 years (std dev ±18.9 years; range, 4–77 years); the mean age at lymphoma diagnosis was 48.8 (std dev ±19.8 years; range 4–81 years.)

Of the 41 subjects with lymphoma with known outcomes, 29 (70%) are known to have died, 27 of these due to this diagnosis. Twelve are alive, in remission or have achieved cure; the current status of 4 subjects is unknown. For those who died, the mean age at death was 55.2 years (std dev 17.8 years; range: 13–83 years). Subjects with lymphoma had significantly higher average baseline serum IgM of 74.5 mg/dl (4–830) than the other subjects in this

cohort, with a serum average of 32.3 mg/dl (range 0–645), ($P = .009$ Mann Whitney test.) (Table S2 summarizes the 49 types of lymphomas noted for these 45 subjects.)

Table 2 provides the patient demographics, baseline immunophenotypes, the lymphoma types, treatment, and outcomes of these subjects. (Previous reports noted the numbers of lymphomas in this cohort, but immunologic and clinical phenotypes, pathology, treatments used, genetics, and outcomes of these patients were not included.[11,30–32] Forty four of these 45 subjects had been diagnosed with a B-cell NHL, one was diagnosed with a T-cell lymphoma. Four of these patients had been previously diagnosed with Hodgkin disease (9%). In three cases, 2 males and one female, Hodgkin lymphoma had been diagnosed at a young age and then NHL subsequently developed as an adult. Of the defined NHL subtypes, diffuse B-cell lymphomas (DLBCL) were the most common type of lymphoma, occurring in 15 subjects (40%) followed by extranodal marginal zone lymphomas (MZL) or mucosa associated lymphomas (MALT) diagnosed in 10 subjects (20%). Three NHL were EBV positive. The T-cell lymphoma occurred in a female with 10 years of nearly asymptomatic hypogammaglobulinemia who then developed leg swelling, and was then found to have an anaplastic lymphoma kinase (ALK)-negative anaplastic, large T-cell lymphoma involving pelvic nodes and bone marrow. Lymphoma sites included the gastrointestinal tract, parotid gland, thyroid, lung, mediastinal lymph, and/or abdominal nodes; one patient developed CNS lymphoma. Treatments included surgical resection, various chemotherapy regimens as these changed over time, radiation, and rituximab (after its approval in 1997). Two males and one female had a stem cell transplant (#14, #20, 43). Subject #20 died shortly post-transplant, subject 43 is alive now 20 years later. The female (#14) with known EBV + DLBCL, is alive, and had a stem cell transplant one year ago. Allogeneic T-Cell therapy[33] was also used in her case.

3.2 | Clinical phenotypes

The patients diagnosed with lymphoma had previously experienced a number of infections characteristic of CVID; however, most patients also had experienced a number of the non-infectious complications commonly found in this immune defect, including autoimmune diseases, enteropathy, lymphadenopathy/ and or splenomegaly, as well as other cancers as summarized on Table 3. Table 4 gives more detailed data for each subject. Autoimmune hemolytic anemia and/or immune thrombocytopenia had been diagnosed in 8 subjects, pancytopenia or hypersplenism in 3 others, pernicious anemia in 2 and primary biliary cirrhosis in 3 subjects. Tissue confirmation of granulomatous disease had been found for 5 patients. Chronic lung disease was known in 11 subjects, three of whom had granulomatous disease found on biopsy. Nine subjects had chronic gastrointestinal disease with malabsorption and/or protein losing enteropathy (20%). Six of the 45 (13%) subjects had also previously been diagnosed with another malignancy.

In the last six years, 17 subjects of these subjects who were available and consented, underwent either whole exome, whole genome, and/or targeted DNA sequencing to identify primary immune deficiency genes (indicated on Table 4). Of these, two subjects (#14 and #30) had genetic defects associated with CVID. One (#14) had a gain of function heterozygous mutation in the p110δ catalytic subunit of the phosphatidylinositol-3-OH

kinase gene, *PI3KCD* (c3061G>A, p.E1021K); the other had a missense mutation (C104R) in *TNFRSF13B* (transmembrane activator and CAML interactor, *TACI*).

3.3 | Subjects not confirmed with lymphoma

Six additional referred CVID patients (4 males and 2 females), had also been diagnosed with a B-cell NHL (Table 5). In these cases, marginal zone lymphoma (MZL) had been diagnosed in 5 subjects (3 extranodal and 2 nodal sites) and 1 with DLBCL. Four of these 6 patients (67%) underwent chemotherapy for lymphoma based on the initial pathologic diagnosis but upon histological re-examination of the diagnostic tissues, immunophenotyping, and molecular/genetic studies at the NCI, these 6 cases were considered not to have lymphoma. The final diagnoses for most cases were either reactive lymphoid or marginal zone hyperplasia. Monoclonal B-cell lymphocytosis (MBL) was diagnosed in one patient. While this a known precursor to chronic lymphocytic leukemia, in the majority, this is less likely to progress to overt malignancy.[34] MBL was established after the 2016 revised fourth edition of the World Health Organization (WHO) classification of lymphoid malignancies; therefore, the peripheral blood clonal B-cell count at the time of his diagnosis was not determined. He remains stable with no evolution of disease now 10 years later. Four of the six misdiagnosed cases had previous evidence of granulomatous infiltrations involving the lung, liver, and/or lymph nodes. Table 3 outlines the clinical and histopathological features of these 6 patients, all of whom are alive. For this group, 4 had genetic studies to identify a gene leading to their underlying immune defect and none were identified.

4 | DISCUSSION

For 647 CVID subjects seen over a 45-year period, 45 (7%) had been diagnosed with a lymphoma, predominately B-cell in origin (96%). One may contrast this with the estimated 2.1% risk of men and women who will be diagnosed with non-Hodgkin lymphoma at some point during their lifetime based on 2016–2018 data.[35]

In this report, we also present the immunologic and clinical phenotypes, treatments, and outcomes of each of these patients and contrast the data of this single-center study with that of other large cohorts, to better understand the phenotypes of patients at risk for this complication. More than half of the patients in the current cohort died due to this complication. First, of these CVID subjects, 67% were females. Female predominance was suggested in earlier studies[11,30] and also in another report.[21] In a previous study, subjects with lymphoma had higher baseline levels of serum IgM than other CVID subjects,[12] also suggested here, as those with lymphoma had significantly higher average baseline serum IgM than other subjects in this cohort. As noted in other studies,[23,36] the majority of the subjects with lymphoma had also experienced a number of other non-infectious complications, including autoimmunity, lymphoid hypertrophy, enteropathy, interstitial lung disease, and/or granulomatous disease. Whether subjects with these complications are at more risk for lymphoma has been suggested,[36] but this would need to be confirmed. In one report, a history of ITP was associated with the development of lymphoma, as it was noted in 8/22 subjects (36.4%).[23] In the current report, a history of ITP was noted for 13% of patients, which however, is comparable to our overall cohort at 14.2%.[11] Granulomatous

inflammation has also been considered as potentially associated with the development of lymphoma.[37] Here, 5 of the 45 (11%) subjects were known to have this tissue pathology, in contrast with 8.1% with no lymphoma, previously noted in this same cohort.[38] In addition to non-infectious complications, 6 of the 45 (13.6%) subjects with lymphoma had previously experienced another malignancy. These added cancers suggest that the mechanisms of chronic immune dysregulation may also be linked to the development of lymphoma in CVID.[39] Aside from the predisposing genetic causes not yet identified in these subjects, chronic infections, antigenic stimulation, excess production of B-cell activation factor (BAFF), and/or increased radio-sensitivity may contribute to abnormal B-cell malignant proliferation.[37,40,41] Although Epstein—Barr virus (EBV) has been linked to a wide range of lymphoproliferative lesions and malignant lymphomas, and in selected congenital immunodeficiencies leads to susceptibility to both infection and lymphoma,[42] in only three of the lymphomas in this cohort the presence of EBV was demonstrated. This may be consistent with another recent publication summarizing 59 CVID cases with lymphoma, in which two (3%) were EBV-associated.[19] In the current report, the 19-year-old female patient (#14) with a mutation in *PI3KCD,* also had high levels of EBV DNA in serum, as noted in others with this gene defect.[43]

Genetic defects have now been identified in 15 to 30% of CVID subjects and are more likely to be identified in subjects with autoimmune or non-infectious inflammatory complications.[28,44,45] Of the 18 subjects tested here, genetic defects associated with CVID were noted in two subjects: the patient with the *PI3KCD* mutation mentioned above, and another patient (#31) with the modifier gene transmembrane activator and CAML interactor (*TACI*). Mutations in the *PI3KCD* gene have been previously associated with lymphoma, affecting 13% of a large cohort.[46] For the *TACI* gene, this is less unclear. Mutations in this gene occur in about 10% of CVID subjects,[45] and were not found in the other subjects with lymphoma genetically tested in this report; however, in another study, 4 of 50 CVID subjects with *TACI* mutations had developed NHL.[47] However, as not all subjects in this report had genetic testing, the data on genetic defects in this cohort may be an underestimate. In another report, 3 of 11 CVID adults with lymphomas had pathogenic mutations in the genes *PMS2*, *PI3KCD*, *CTLA4,* and one other had a mutation in *TACI*.[23]

In addition to these subjects, 6 other referred CVID patients had also been diagnosed with a B-cell lymphoma (5 with marginal zone lymphoma and one with diffuse large B-cell lymphoma), of whom 4 had already undergone some form of treatment for this Table 5 However, after review of the original pathology in these cases, these diagnoses were revised. Four of these 6 cases were diagnosed with either lymphoid or marginal zone hyperplasia. Lymphoid hyperplasia with striking lymphadenopathy, splenomegaly, and lymphoid infiltrates in tissues are commonly observed in CVID and could be confused with lymphoma. B-cell lymphomas are generally characterized by monoclonal expansions, demonstrated by flow cytometry or molecular studies for immunoglobulin (Ig) gene rearrangement. However, in CVID, B-cell clonal expansions occur in patients without malignancy.[48–50] In addition, clonal rearrangements of the immunoglobulin heavy chain (IgH) and the T-cell receptor (TCR) can lead to oligoclonal lymphocyte populations, irrespective of histology.[51] Possibly, underlying these observations is that the intrinsic B-cell defects in CVID lead to an expansion of naïve unmutated B-cells, loss of B-cell receptor

somatic hypermutations, and clonal B-cell expansion.[50] This clonal restriction is not limited to B-cells as the structure and composition of the TCR β chain also shows less junctional diversity, fewer n-nucleotide insertions and deletions, and lack of the highly modified TCRs seen in healthy controls.[52] For these reasons, detection of monoclonal or oligoclonal B- or T-cell populations cannot be used to confirm the diagnosis of lymphoma in CVID without comprehensive pathology review.[15] In lymph nodes, germinal center morphology may be distorted, with a lack of well-developed lymphoid cuffs with atypical hyperplasia.[15,53] Lymphoid hyperplasia during infections in extranodal sites may also clinically mimic lymphoma.[53] CVID subjects with autoimmunity may have lymph nodes with particularly irregularly shaped and hyperplastic germinal centers.[54] The spleen in CVID may also show nonspecific, white-pulp hyperplasia with reactive follicles, giant follicles, marginal zone hyperplasia, and clustered histiocytes in variously formed granulomata.[55,56] Four of the six misdiagnosed subjects had granulomatous infiltrations in organs and or lymph nodes, suggesting that this adds further complexity to these histologic features.

There are clear limitations of this report, the first being referral bias. The immune deficiency practice described here, had its origin at a known cancer center, and the first 12 patients were from this group. While subjects were referred for the pre-existing CVID immune defect, this referral location could still inflate the incidence of NHL in this study. However, these data are in agreement with the numbers of two other single-center studies.[24,26] Second, not all pathology material was available for re-examination, thus more of these subjects may have been incorrectly assigned. Some patients were followed long-term while others were seen for a shorter periods in consultation, thus the current outcome for 4 subjects is not known. Given the nature of this retrospective study, spanning 4 decades, classification guidelines for lymphoid malignancies have been continuously modified as improved understanding of lymphoma biology and identification of cellular and molecular markers has evolved. As such, further subtyping of many of the earlier lymphomas was not possible. Similarly, over this long time span, treatment modalities have been markedly altered and improved, thus treatment outcomes are likely to be improved for currently diagnosed patients. Finally, due more recent availability, genomic testing by whole exome sequencing, was done only for a limited number of patients. Further application of genomics to the study of CVID lymphomas may lead to improved care of these patients and may advance our understanding of lymphomagenesis in this immune deficiency.

5 | CONCLUSIONS

This study highlights the high prevalence of lymphoma in this large cohort of CVID patients followed for some decades and presents the immunologic data, clinical features, treatment, and outcomes over this time. An additional feature of this study is that the diagnosis of lymphoma can be challenging in CVID patients due to the co-existing immunologic tissue pathology. While CVID patients require close clinical follow up, lymphomas may arise in both lymphoid tissue and in extranodal locations, making routine screening recommendations difficult. With continued reports such as this and others characterizing malignant complications in CVID, collective discussion among clinical immunologists, oncologists and pathologists, a potential consensus toward guidelines for surveillance, diagnosis, and clinical management may emerge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance Statement

One of the more common of the genetic immune defects is common variable immune deficiency. The main problem is lack of an ability to produce functional immune globulins and a severe defect of antibody production. These results in infections but one of the other complications is the development of lymphoma, a significant cause of death. The kind of lymphoma that develops, how often and in which patients who were seen at one large medical center in New York over 4 decades, is the topic of this article. We also include some cases in which lymphoma was diagnosed, but in these cases, this diagnosis was later retracted as it was an error.

TABLE 1

Incidence of lymphoma in common variable immunodeficiency (CVID)

Studied group	CVID cohort number	Publication year	Diagnosed lymphoma (%)	Comments
United Kingdom[57]	220	1985	1.4%	3 NHL **
Sweden and Denmark[21]	176	2002	2.3%	4 NHL
Italy[58]	224	2007	1.8%	4 NHL
ESID +[12]	334	2008	0.9%	3 NHL
Mount Sinai[11]	473	2012	8.2%	39 NHL
ESID +[22]	902	2014	2.5%	25 NHL
Prague[23]	295	2018	3.7%	4 NHL; 5 HD; 2 T-cell lymphoma
ESID +[14]	972	2018	3.8%	Lymphomas not otherwise specified
Italy[24]	455	2018	8.4%	33 NHL; 5 HD
USIDNET *[20]	1,285	2018	2.9%	37 NHL
Duke University[26]	198 (91 pediatric-onset; 107 adult-onset)	2019	9.1%	18 NHL/leukemia

Note:

+ ESID: European Society for Immunodeficiencies; HD: Hodgkin lymphoma.

* USIDNET: United States Immunodeficiency Network.

** NHL: non-Hodgkin lymphoma.

TABLE 2

CVID Subjects with lymphoma, location, treatment and outcomes

Subject	Age at lymphoma diagnosis (years)/sex	Lymphoma type (subtypes or cell-of-origin when known)	Location/Site	Treatment & outcomes (Regimen specified when known)	Age at death (years) or alive, age
1	40/M	NHL, B-cell NOS	Stomach	Died due to lymphoma-related complications	Died age 42
2	62/M	EBV$^+$ DLBCL, NOS	Spleen, lymph nodes	Chemotherapy; Died due to lymphoma-related complications	Died age 62
3	74/M	DLBCL (Germinal Center B-cells)	Mediastinum	Died due to lymphoma-related complications	Died age 74
4	1st 4 M	1st: Hodgkin lymphoma	NA	Chemotherapy	Died age 25
	2nd 24/F	2nd: NHL, B-cell	Lymph nodes	Died due to lymphoma-related complications	
5	59/F	MALT	Parotid gland	NA	Alive at last encounter
6	46/F	Extranodal MZL	Lung	No treatment given; Died due to complications of PML	Died age 48
7	53/M	DLBCL (T-cell/histiocyte rich B-cell lymphoma)	Liver	Chemotherapy	Alive age 73
8	81/F	NHL, B-cell	Jejunum	Chemotherapy Died due to lymphoma-related complications	Died age 83
9	38/M	Extranodal MZL	Abdomen	Chemotherapy; Died due to lymphoma-related complications involving lung, liver and malnutrition	Died age 38
10	71/F	DLBCL, NOS	Lung, lymph nodes	C-MOPP; Died due to lymphoma-related complications	Died age 72
11	43/M	DLBCL, NOS	Small bowel	Surgical resection and chemotherapy	Alive age 53
12	42/F	NHL, B-cell	Lymph nodes	Chemotherapy; Died due to lymphoma-related complications	Died age 42
13	NA/F	Extranodal; MZL	Lung	NA	Alive at last encounter
14	19/F	DLBCL; EBV+	Lymph nodes supraclavicular	DA-EPOCH; R-COPAD; EBV CTL therapy, bone marrow transplant	Alive at 20
15	71/F	DLBCL, NOS	Thyroid	CHOP	Alive age 71
16	1st 56	1st MALT	Parotid gland	Surgical parotid node removal and RT	Died age 71
	2nd 67/F	2nd Follicular B-cell lymphoma	Axilla and mediastinum	R-CHOP; Died due to lymphoma-related complications	
17	11/M	Hodgkin lymphoma	Lung	MOPP-ABVD	Alive age 35
18	NA/F	NHL, B-cell	NA	NA	Alive at last encounter
19	34/F	MALT	Cheek, parotid gland	Surgical node removal, no chemotherapy	Alive age 54
20	1st child	1st Hodgkin lymphoma	NA	Chemotherapy	Died age 41

Subject	Age at lymphoma diagnosis (years)/sex	Lymphoma type (subtypes or cell-of-origin when known)	Location/Site	Treatment & outcomes (Regimen specified when known)	Age at death (years) or alive, age
	2nd 39/M	2nd: NHL, B-cell	Brain	CHOP and stem cell transplantation; Died due to lymphoma-related complications	
21	51/F	DLBCL, NOS	Lung, lymph nodes	Chemotherapy; Died due to lymphoma-related complications	Died age 55
22	56/F	DLBCL NFIL (Intermediate-grade diffuse, small-cleaved cell)	Lymph nodes (pelvic)	M-BACOD, CHOP, CP, RT	Alive at last encounter
23	41/M	DLBCL, NOS	Lymph nodes (abdominal and pelvic)	R-CHOP	Alive age 51
24	48/F	DLBCL, NOS	Proximal jejunum	Surgical resection	Died, age 50 of other causes
25	46/M	MALT lymphoma	Parotid	not treated	Died age 48
26	1st 10	1st Hodgkin lymphoma	NA	Chemotherapy	Died age 26
	2nd 25/M	2nd NHL, B-cell	Lymph nodes	CHOP; Died due to complications related to undiagnosed neurodegenerative disease	
27	53/F	DLBCL, NOS	Pelvis, spine	R-CHOP	Alive age 57
28	77/M	NHL, B-cell	Lymph node	Chemotherapy; Died due to lymphoma-related complications	Died age 79
29	43/F	Extranodal MZL	Kidney	Partial nephrectomy; R-CHOP	Alive age 46
30	70/F	NHL, B-cell	Lung	Chemotherapy; Died due to lymphoma-related complications involving severe lung disease	Died age 72
31	45/M	Plasmacytoid lymphoma, IgA+	Jejunum	Surgical resection; R-CHOP; Died due to lymphoma-related complications	Died age 47
32	65/F	DLBCL, NOS	Diffuse, bone marrow	CHOP; Died due to lymphoma-related complications	Died age 67
33	NA/F	NHL, B-cell	NA	Chemotherapy	Died age 67
34	51/M	DLBCL, NOS	Lymph nodes	Chemotherapy; Died due to lymphoma-related complications	Died age 57
35	66/F	EBV^{+} T cell rich DLBCL, NOS	NA	NA	Died age 68
36	59/F	DLBCL, Intermediate-grade NHL (Diffuse, mixed small and large cell)[b]	Lung	RT, Chemotherapy; Died due to lymphoma-related complications	Died age 65
37	54/F	DLBCL, Intermediate-grade NHL (Diffuse, mixed small and large cell)[b] DLBCL, NOS; IgM-kappa macroglobulinemia	Lymph nodes (pelvic)	Chemotherapy; Died due to lymphoma-related complications	Died age 58
38	64/F	DLBCL, NOS	Supraclavicular area and abdomen	C-MOPP; Died due to lymphoma-related complications	Died age 68
39	58/F	DLBCL, Intermediate-grade NHL (Diffuse, mixed small and large cell)[b]	Right inguinal lymph node	Surgical resection, CHOP; Died 15 years later due to unrelated causes	Died age 69

Subject	Age at lymphoma diagnosis (years)/sex	Lymphoma type (subtypes or cell-of-origin when known)	Location/Site	Treatment & outcomes (Regimen specified when known)	Age at death (years) or alive, age
40	75/F	Anaplastic large T-cell lymphoma, ALK-negative	Lymph nodes (pelvic)	CHOEP, ICE	Alive age 80
41	46/F	Extranodal MZL; MBL	Abdominal mass above kidney	R-CHOP, 4 years after diagnosis	Alive age 55
42	12/F	DLBCL, NOS	Liver, spleen	CHOP; Died due to lymphoma-related complications	Died age 13
43	46/M	MALT	Lung	CVP–R, stem cell transplantation	Alive age 64
44	34/F	DLBCL, NOS	Lymph nodes (pelvic)	R-CHOP	Alive age 37
45	68/F	DLBCL, NOS	Lung, lymph nodes	R-EPOCH	Alive age 72

Note: Abbreviations: ABVD, doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine; ALK, Anaplastic lymphoma kinase; CHOEP, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), etoposide, prednisone; CHOP, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), prednisone; C-MOPP, cyclophosphamide, vincristine (oncovin), procarbazine, prednisone; CP, chlorambucil, prednisone; CVP, cyclophosphamide, vincrinstine, prednisone; DA=dosage adjusted; DLBCL, diffuse B-cell lymphoma (NOS, not otherwise specified); HD, Hodgkin lymphoma; ICE, ifosfamide, carboplatin, etoposide; MALT, mucosal-associated lymphoid tissue; M-BACOD, high-dose methotrexate, bleomycin (adriamycin), doxorubicin, cyclophosphamide, vincristine (oncovin), dexamethasone; MBL, Monoclonal B-Cell Lymphocytosis; MOPP, nitrogen mustard, vincristine (oncovin), procarbazine, prednisone; MZL, marginal zone lymphoma; NA, information not available; NHL, non-Hodgkin lymphoma; PML, Progressive multifocal leukoencephalopathy; R-CHOP, rituximab, cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin), prednisone; R-COPAD, (rituximab, cyclophosphamide, vincristine, prednisolone and doxorubicin); R-EPOCH, rituximab, etoposide, prednisone, vincristine (oncovin), cyclophosphamide, doxorubicine (hydroxydaunomycin); R-EPOCH, rituximab, etoposide, prednisone, vincristine, oncovin, cyclophosphamide, doxorubicin; RT, radiation therapy.

[a]Diagnosis was made prior to the fourth edition World Health Organization (WHO) classification.

[b]Classification according to the National Cancer Institute's Working Formulation (IWF) (Rosenberg et. al 1982)

TABLE 3

Summary of other medical conditions

Other features	Numbers	Percent
Splenomegaly, lymphadenopathy	11	24
Enteropathy with or without malabsorption	9	20
Interstitial lung disease, bronchiectasis	8	18
Other Autoimmunity: primary biliary cirrhosis (3), pernicious anemia (2), alopecia (1), vasculitis (1), rheumatoid arthritis(1)	8	18
Other cancers (Hodgkin lymphoma, thyroid adenoma, vaginal cancer	7	16
Immune Thrombocytopenia	6	13
Granulomatous disease (lung or nodes or both)	5	11
Autoimmune hemolytic anemia	1	2

TABLE 4

Immunologic and Clinical Features

dCase	Age at CVID diagnosis	IgG Baseline mg/dl	IgA Baseline mg/dl	IgM Baseline mg/dl	Recurrent infections	Autoimmunity; Lympho-proliferation features	Other features	Other cancers
1	36 (M)	50	0	25	Recurrent infections	AIHA; Splenomegaly		
2	58 (M)	NA	9	29	Cryptococcal lung disease, skin abscesses, pyoderma of legs	Vasculitis; Splenomegaly		
3[a]	67 (M)	267	<7	45	Chronic bronchitis		Chronic obstructive pulmonary disease, chronic schizophrenia	
4	4 (F)	90	0	400	Recurrent pneumonia, Hepatitis C		Malabsorption, malnutrition	Hodgkin disease age 8
5[a]	3 35 (F)	307	28	15	Recurrent infections	ITP Lymphadenopathy	Lung nodules	
6[a]	13 (F)	180	23	15	Pneumonias; progressive multifocal leuko- encephalopathy	ITP	Malabsorption, diarrhea bronchiectasis	
7[a]	51 (M)	317	38	142	Sinusitis	Splenomegaly		
8	64 (F)	110	3	46	Recurrent respiratory tract infections; Inner ear abscess, otitis, sinusitis, pneumonias,	Pancytopenia, pernicious anemia	Malabsorption, osteoporosis, atrophic gastritis	Thyroid adenoma
9[a]	24 (M)	42	8	10	Pneumonias	Recurrent ITP	Bronchiectasis, Interstitial lung disease;	
10	65 (F)	354	20	116	Lung infections		Chronic lung disease Bronchiectasis	
11[a]	30 (M)	39	0	10	Pneumonias, sinusitis, joint infection	Splenomegaly	Enteropathy; malabsorption	
12	42 (F)	464	8	84	Recurrent infections	Pancytopenia, Pernicious anemia	Malabsorption	
13	59 (F)	<33	<6	10	Recurrent pneumonias bronchitis, sinusitis,		Granulomatous lung disease; interstitial lung disease	
14[a]	5 (F)	450	<5	160	Mild respiratory infections I infections	Lymphadenopathy, Gastrointestinal nodular hyperplasia, splenomegaly	Enteropathy; growth failure	
15[a]	60 (F)	387	14	29	Recurrent infection; pneumonia			
16	46 (F)	276	0	160	Recurrent infections; stomatitis, glossitis			

dCase	Age at CVID diagnosis	IgG Baseline mg/dl	IgA Baseline mg/dl	IgM Baseline mg/dl	Recurrent infections	Autoimmunity; Lympho-proliferation features	Other features	Other cancers
17[a]	32 (M)	<30	<5	26	Recurrent lung infections; sinus and ear infections			Hodgkin disease age 11
18	26 (F)	245	10	63				
19	31 (F)	101	7	11	Lung infections		Segmental bronchiectasis	
20	34 (M)	253	22	131	Recurrent infections	Primary biliary cirrhosis	Splenectomy	Hodgkin disease earlier
21	51 (F)	200	10	65	Chronic lung disease	Splenomegaly	Severe bronchiectasis	
22	55 (F)	380	66	35	Recurrent infections		Protein loosing enteropathy;	
23[a]	39 (M)	267	49	20	Recurrent infections	Recurrent ITP		
24	45 (F)	NA	34	5	Lung infections, otitis, sinusitis	Bronchiectasis	Nodular lymphoid hyperplasia, malabsorption	Carcinoma of the vagina
25[a]	46 (M)	113	<5	6	Lung infections	Splenomegaly Hypothyroidism Primary Biliary Cirrhosis	Granulomatous lung disease	
26	8 (M)	105	34	5	Recurrent sinusitis	Juvenile Rheumatoid arthritis; ITP	Splenectomy	Hodgkin disease as a child
27[a]	50 (F)	266	<5	<5	Frequent respiratory tract infections/Asthma			
28	77 (M)	266	<5	<5	Asthma, recurrent pneumonia,			
29	38 (F)	253	16	47	Recurrent infections			
30	71 (F)	512	6	nl	Recurrent respiratory tract infections			
31[a]	11 (M)	6	21	16	Recurrent respiratory tract infections; giardiasis	ITP; Splenomegaly	Lung nodules. Bronchiectasis,	
32	62 (F)	175	10	150	Recurrent pneumonia, severe sinusitis, Hepatitis C			
33	26 (F)	73	10	150	Sinusitis, pneumonia			
34	45 (M)	120	<8	40	Asthma, recurrent pneumonias,	Hypersplenism		
35[a]	60 (F)	NA	33	44	*Pneumocystis carinii* Pneumonia, sinusitis		Gastritis	
36	53 (F)	175	0	830	Recurrent respiratory tract infections, Recurrent pneumonia			

dCase	Age at CVID diagnosis	IgG Baseline mg/dl	IgA Baseline mg/dl	IgM Baseline mg/dl	Recurrent infections	Autoimmunity; Lympho-proliferation features	Other features	Other cancers
37	50 (F)	126	0	84	Recurrent pneumonia			
38	64 (F)	200	20	11	Recurrent infections	AIHA	Malabsorption	
39	40 (F)	214	0	96	Recurrent infections	Rheumatoid arthritis, Primary biliary cirrhosis	Chronic hepatitis, coronary artery disease	
40[a]	64 (F)	190	60	90	Mild infections			
41[a]	30 (F)	9	<7	<7	Frequent respiratory tract infections, bronchitis, Herpes zoster	Interstitial lung disease, lymphadenopathy	Lung nodules;	
42	10 (F)	162	2	26	Recurrent infections/Suppurative parotitis and otitis		Lung nodules; Granulomatous disease; lung and nodes	
43	44 (M)	277	18	26	Viral meningitis	Alopecia areata		
44[a]	32 (F)	335	<5	50	Mastitis, shingles		Lung nodules; Granulomatous disease nodes	
45[a]	63 (F)	215	<5	18	Shingles	Splenomegaly Hyperthyroid,	Granulomatous lung disease, Psoriasis	

Note: Abbreviations: AIHA, autoimmune hemolytic anemia; ITP, immune thrombocytopenia; NA, not available.

[a]Whole exome sequence analysis was performed for gene mutations for established immune defects.

TABLE 5

Clinical and histopathologic features of CVID for whom the diagnosis of lymphoma was reversed

Case	Age at CVID diagnosis in years (gender)	Recurrent infections	Autoimmune; lymphoproliferation features	Other features	Baseline Ig levels (mg/dl)	Malignant diagnosis (age at biopsy)	Biopsy site: pathological features concerning for malignancy	Course of Chemotherapy	Final diagnosis
1	46 (M)	Sinusitis Bronchitis Pneumonia	AIHA, ITP, Splenomegaly	Enteropathy, Granulomatous lung and liver disease	IgG: 114 IgA: 14 IgM: 9.7	MZL (63)	Bone marrow: kappa B-cell predominance and IgH clonal increase	No	Monoclonal B-cell lymphocytosis
2[a]	45 (M)	Bronchitis Pneumonia Shingles	Axillary LAD Abdominal LAD	Enteropathy	IgG: 107 IgA: <6 IgM: <6	MZL (48)	R axillary LN: kappa B-cell predominance and IgH clonal increase	Rituximab	Marginal zone hyperplasia
3[a]	37 (M)	Sinusitis Bronchitis Pneumonia Shingles	AIHA, ITP; Splenomegaly Diffuse LAD		IgG: 186 IgA: 9 IgM: 24	MZL (42)	Bone marrow: lambda B-cell predominance, no IgH clonal increase	R-bendamustine, Rituximab	Normocellular bone marrow with progressive tri-lineage hematopoiesis, scattered interstitial lymphocytes present, no atypical cell population identified, no morphological evidence of lymphoma
4	28 (F)	Sinusitis Bronchitis Pneumonia Giardia	AIHA, ITP; Splenomegaly Diffuse LAD	Granulomatous liver and lung disease, Enteropathy	IgG: <6 IgA: <6 IgM: 22	DLBCL (37)	Cervical LN: B-cell lymphocytosis, clonal B-cell population with excess kappa light chain	Cytoxan, Prednisone and Vincristine	Reactive lymphoid hyperplasia
5[a]	25 (F)	Sinusitis, Bronchitis Streptococcal pharyngitis Mycoplasma pneumonia EBV; Shingles Parvovirus Norovirus	Lymphopenia, neutropenia, ITP; Splenomegaly	Enteropathy Granulomatous lung disease	IgG: <15 IgA: <7 IgM: <6	MZL (27)	Lung and node: atypical morphologic features of lymphocytes, polytypic light chain expression with IgH clonal increase	Rituximab	Nodular lymphoid hyperplasia, clusters of histocytes with ill-defined and poorly formed granulomas
6[a]	43 (M)	Chronic respiratory infections, fevers	Primary biliary cholangitis; Hashimoto thyroiditis; Splenomegaly	Liver and bone marrow granulomatous disease; interstitial lung disease with hypoxemia.	IgG: 116 IgA: <5 IgM: 6	MZL (47)	Right parotid gland and lymph node	Rituximab given only for granulomatous disease only	Atypical marginal zone hyperplasia

Note: Abbreviations: AIHA, autoimmune hemolytic anemia; DLBCL, diffuse B-cell lymphoma; ITP, idiopathic thrombocytopenia; LAD, lymphadenopathy; LN, lymph node; MZL, marginal zone lymphoma.

[a]Whole exome sequence analysis was performed for gene mutations for established immune defects