Clinicopathological characteristics of T-cell non-Hodgkin lymphoma arising in patients with immunodeficiencies: a single-center case series of 25 patients and a review of the literature

Marieke L. Nijland,[1#] Lianne Koens,[2#] Steven T. Pals,[3] Ineke J.M. ten Berge,[1] Frederike J. Bemelman[1] and Marie José Kersten[4*]

[1]Renal Transplant Unit, Department of Nephrology, Academic Medical Center; [2]Department of Pathology, Academic Medical Center; [3]Department of Pathology and Lymphoma and Myeloma Center Amsterdam (LYMMCARE), Academic Medical Center and [4]Department of Hematology and Lymphoma and Myeloma Center Amsterdam (LYMMCARE), Academic Medical Center, Amsterdam, the Netherlands

[#]MLN and LK contributed equally to this work.

Haematologica 2018
Volume 103(3):486-496

ABSTRACT

Although it is known that B-cell lymphomas occur more frequently in immunocompromised patients, thus far such an association has not been clearly established for T-cell lymphomas. Of the 251 patients who were diagnosed with a T-cell non-Hodgkin lymphoma in our center between 1999 and 2014, at least 25 were identified in immunocompromised patients. Herein, we retrospectively analyzed the clinical and pathological characteristics of these 25 cases. In addition, we searched the literature and present an overview of 605 previously published cases. The actual number of patients with B-cell chronic lymphocytic leukemia and patients on immunosuppressive drugs for inflammatory bowel disease or rheumatoid arthritis in the total cohort of 251 patients diagnosed with T-cell non-Hodgkin lymphoma was much higher than the number of patients expected to have these diseases in this cohort, based on their prevalence in the general population. This, together with the large number of additional cases found in the literature, suggest that the risk of developing T-cell non-Hodgkin lymphoma is increased in immunocompromised patients. Compared to T-cell non-Hodgkin lymphoma in the general population, these lymphomas are more often located extranodally, present at a younger age and appear to have a poor outcome. The observations made in the study herein should raise awareness of the possible development of T-cell non-Hodgkin lymphoma in immunodeficient patients, and challenge the prolonged use of immunosuppressive drugs in patients who are in clinical remission of their autoimmune disease.

Correspondence:

m.j.kersten@amc.uva.nl

Received: May 3, 2017.

Accepted: December 13, 2017.

Pre-published: December 21, 2017.

doi:10.3324/haematol.2017.169987

Check the online version for the most updated information on this article, online supplements, and information on authorship & disclosures: www.haematologica.org/content/103/3/486

Introduction

It has long been recognized that patients with either a primary or acquired immunodeficiency are at increased risk for the development of malignant lymphomas.[1,2] Hematopoietic stem cell and solid organ transplant recipients, for example, can develop post-transplant lymphoproliferative disease (PTLD);[3] patients infected with the human immunodeficiency virus (HIV), patients with primary immunodeficiencies and patients treated for inflammatory bowel disease (IBD) with immunosuppressive drugs all have an increased risk for developing lymphoma.[4-8] Moreover, this complication is seen in patients with autoimmune diseases like rheumatoid arthritis (RA), primary Sjögren syndrome and systemic lupus erythematosus. However, it is not clear whether the lymphomas in these patients are triggered by chronic inflammation caused by the disease itself or by the (immunosuppressive) therapies used.[9-13] In all the groups studied, the reported lymphomas are predominantly of B-cell origin.[3,5,11]

Table 1. Patient characteristics.

Primary disorder		Sex	Age at Dx	Disorder defined	Location lymphoma	Histologic subtype	Staging*	Prior IS drugs or chemotherapy	Period given	Interval start IST- Dx (m)
AI diseases	1	male	23	CD	Kidney	Precursor T-LBL	IE	Prednisolone	NR	NR
								Azathioprine	> 2 y	NR
	2	female	20	CD and PSC	Skin	Primary C-CD30+ T-LPD	IA	Adalimumab	1-2 y	NR
	3	male	46	CD	Liver	HSTCL	IV	Azathioprine	NR	NR
	4	male	21	CD	Spleen, BM, liver	PTCL, NOS	IV	Azathioprine	> 2 y	44
								Prednisolone	NR	NR
	5	male	39	CD	LN	Precursor T-LBL	III	Azathioprine	> 2 y	210
	6	male	43	CD	Small bowel, kidneys, pancreas, heart	PTCL, NOS	IV	Prednisolone	NR	NR
								Azathioprine	> 2 y	NR
								Infliximab	1-2 y	NR
								Adalimumab	> 2 y	NR
	7	female	36	CD	LN, pelvic cavity, skin	ALCL, ALK-	II	Azathioprine	> 2 y	173
	8	female	40	RA	Nasopharynx	ENKL, nasal type	II	Methotrexate	> 2 y	NR
	9	male	52	RA	Skin	Mycosis Fungoides	IA	Etanercept	1-2 y	18
	10	female	75	RA	LN, spleen, liver	AITL	IV	Methotrexate	6-12 m	6
	11	male	70	PMR	LN, spleen, bone	AITL	IV	Prednisolone	> 2 y	60
	12	male	54	M. Sjögren	Skin	Mycosis Fungoides	IA	Prednisolone	1-2 y	13
	13	male	43	Sarcoidosis	LN, liver	AITL	III	NR		
	14	male	46	PSC	LN	ALCL, ALK+ (small cell variant)	II	Prednisolone	> 2 y	NR
Hematologic malignancy	1	male	81	B-CLL	PB	T-PLL	IV	Chlorambucil	NR	92
	2	male	62	B-CLL	Skin	Primary C-CD30+ T-LPD	IA	NR		
	3	male	78	B-CLL, AIHA and MN	LN, spleen, BM	PTCL, NOS	IV	Chlorambucil	NR	NR
								Prednisolon	NR	NR
								Cyclophosphamide	NR	NR
								Rituximab	NR	NR
								PI3K-inhibitor	1-2 y	21
	4	male	59	Multiple myeloma and ASCT	BM, spleen, liver	PTCL, NOS	IV	Cyclophosphamide	6-12 m	10
								Prednisolone	NR	NR
								CT, multiple courses	NR	143
	5	male	75	Mantle cell lymphoma	LN, lung	ALCL, ALK-	IV	Cyclophosphamide	3-6 m	13
								Rituximab	3-6 m	13
								Fludarabine	3-6 m	13
								Peginterferon	6-12 m	NR
	6	male	75	B-CLL	Spleen	PTCL, NOS	III	Chlorambucil	> 2 y	165
Organ transplantation	1	male	70 MN	Kidney Tx,	Medulla oblongata, pons	Clonal T-cell population in liquor, CNS lymphoma at imaging	IV	MMF	<3 m	5
								Prednisolone	3-6 m	5
								Tacrolimus	3-6 m	5
								Chlorambucil	NR	NR
								Cyclophosphamide	NR	NR
								Prednisolone	NR	NR
	2	male	71	Kidney Tx	Small bowel	ALCL, ALK-	IIIE	Prednisolone	> 2 y	367
								MS	> 2 y	367
								Azathioprine	> 2 y	367
								Tacrolimus	> 2 y	367
	3	female	46	Liver Tx	LN, bone marrow	EBV+ PTCL, NOS	IV	Tacrolimus	> 2 y	95
	4	male	78	Kidney tx	Small bowel	T-NHL, unclassifiable	IV	Prednisolone	> 2 y	315
								Azathioprine	> 2 y	315
HIV	1	male	26	HIV	LN, lung	ALCL, ALK-	II	None		

*For cutaneous lymphomas the tumor-node-metastasis-blood (TNMB) system was used. All other lymphomas were staged by the Ann Arbor staging system. AI: autoimmune; AIHA: autoimmune hemolytic anemia; AITL: angioimmunoblastic T-cell lymphoma; ALCL: T-cell anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; ASCT: autologous stem cell transplant; B-CLL: B-cell chronic lymphatic leukemia; BM: bone marrow; CT: chemotherapy; CD: Crohn's disease; Dx: diagnosis; EBV: Epstein-Barr virus; ENKL: extranodal NK/T-cell lymphoma; HIV: human immunodeficiency virus; HSTCL: hepatosplenic T-cell lymphoma; IQR: interquartile range; IS(T): immunosuppressive (therapy); LN: lymph nodes; MMF: mycophenolate mofetil; MS: mycophenolate sodium; MN: membranous nephropathy; NR: not recorded/retraceable; PB: peripheral blood; PMR: polymyalgia rheumatica; Primary C-CD30+ T-LPD: primary cutaneous CD30+ T-cell lymphoproliferative disease; PSC: primary sclerosing cholangitis; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; RA: rheumatoid arthritis; T-LBL: T-cell lymphoblastic lymphoma; T-PLL: T-cell prolymphocytic leukemia; T-NHL: T-cell non-Hodgkin lymphoma; Tx: transplantation.

Much less is known about the development of T-cell non-Hodgkin lymphomas (T-NHL) in patients with immunodeficiencies or autoimmune diseases. For HIV patients and solid organ transplant recipients some large case series and reviews on T-NHL have been published.[14-20] In IBD patients, the development of a specific and rare subtype of T-NHL, hepatosplenic T-NHL (HSTCL), has been associated with the use of thiopurines, either alone

Table 2. Patient and lymphoma characteristics, ordered by primary disorder.

Disorder	AI disease	Hematologic malignancy	Solid organ Tx	HIV	Total
Number of cases	Total: 14 CD: 7 (50%) RA: 3 (21.4%) Sarcoidosis: 1 (7.1%) PR: 1 (7.1 %) M. Sjogren: 1 (7.1%) PSC: 1 (7.1%)	Total: 6 B-CLL: 4 (66.7%) MCL: 1 (16.7%) MM: 1 (16.7%)	Total: 4 Kidney: 3 (75%) Liver: 1 (25%)	Total: 1	25
Median age Dx (y [IQR])	43 (33-53)	75 (61-79)	71 (52-76)	26	52 (40-73)
Sex					
Male	10 (71.4%)	6 (100%)	3 (75%)	1 (100%)	20 (80%)
Female	4 (28.6%)	–	1 (25%)	–	5 (20%)
IS therapy or chemotherapy	IST: 13 (92.9%) NR: 1 (7.1%)	CT: 5 (83.3%) NR:1 (16.7%)	IS: 4 (100%)	No IS: 1(100%)	IST: 17 (68%) CT: 5 (20%) No IST: 1 (4%) NR: 2 (8
Median interval start drugs – Dx (m [IQR])	44 (13-173)	92 (17-154)	205 (27.5-354)	–	76 (14,3-171)
Duration of IST or CT (treatment longest given)	3-6 m:- 6-12 m:1 (7.1%) 1-2 y: 3 (21.4%) >2 y: 8 (57.1%) NR: 2 (14.3%)	3-6 m: - 6-12 m: 2 (33.3%) 1-2 y: 1 (16.7%) >2 y: 1 (16.7%) NR: 2 (33.3%)	3-6 m: 1 (25%) 6-12 m: - 1-2 y: - >2 y: 3 (75%) NR: -	–	3-6 m: 1 (4%) 6-12 m: 3 (12%) 1-2 y: 4 (16%) >2 y: 12 (48%) NR: 4 (16%)
Histologic subtype	CTCL: 3 (21.4%) AITL: 3 (21.4%) PTCL, NOS: 2 (14.3%) Prec T-LBL: 2 (14.3%) ALCL, ALK+ : 1 (7.1%) ENKL: 1 (7.1%) HSTCL: 1 (7.1%) ALCL, ALK-: 1 (7.1%)	PTCL, NOS: 3 (50%) CTCL: 1 (16.7%) ALCL, ALK-: 1 (16.7%) T-PLL : 1 (16.7%	PTCL, NOS: 1 (25%) T-NHL, unclass: 1 (25 %) ALCL, ALK-: 1 (25%) Clonal T-cell population in liquor: 1 (25%)	ALCL, ALK-: 1 (100 %)	PTCL, NOS: 6 (24%) ALCL, ALK-: 4 (16%) AITL:3 (12%) CTCL: 4 (16%) Prec T-LBL: 2 (8%) ALCL, ALK+ : 1 (4%) ENKL: 1 (4%) HSTCL: 1 (4%) T-PLL: 1 (4%) Clonal T cell population in liquor: 1 (4%) T-NHL, unclass: 1 (4%)
Location	LN: 5 (35.7%) EN: 13 (92.9%) Exclusive EN: 9 (64.2%)	LN: 3 (50%) EN: 5 (83.3%) Exclusive EN: 3 (50%)	LN: 1 (25%) EN: 4 (100%) Exclusive EN: 3 (75%)	LN: - EN: 1 (100%) Exclusive EN: 1 (100%)	LN: 9 (36%) EN: 23 (92%) Exclusive EN: 16 (64%)

continued in the next page

or in combination with tumor necrosis factor (TNF)-α inhibitors.[21,22] Even less is known about the development of T-NHL in patients with other immunodeficiencies, as only case reports and some small case series have been published.

Herein, we present a relatively large series of 25 immunodeficient patients in whom T-NHL was diagnosed in a single referral center in the period 1999 to 2014. In this cohort study, we describe the clinical characteristics of these cases and correlate them to the pathological features of T-NHL. Furthermore, we present a review of the literature on T-NHL in immunocompromised patients. To the best of our knowledge, this is the largest series of T-NHL in patients with varying causes of immunodeficiency reported so far.

Methods

Histopathological material and reports from patients treated in or referred to the Academic Medical Center in Amsterdam are stored prospectively in a database. This database was queried for samples on which a T-cell receptor (TCR) gene rearrangement analysis was performed between 1999 and 2014. In our center, analysis of TCR gene rearrangement on tumor tissue is standard practice in the workup if T-NHL is suspected. In cases where the diagnosis of T-NHL was confirmed by histology, molecular testing and clinical features, the corresponding clinical data were searched for the presence of immunodeficiency prior to the diagnosis of T-NHL. For all cases, the biopsies were reviewed and immunohistochemical stains for CD2, CD3, CD4, CD5, CD8, granzyme B, PD1, CD30, ALK1, CD21, CD20, TdT, CD56 and *in situ* hybridization for Epstein-Barr virus (EBV)-encoded coded ribonucleic acid (RNA; EBER) were analyzed. If these were not performed in the routine diagnostic work-up (especially in older cases), they were additionally performed for this purpose. The lymphomas were (re)classified according to the World Health Organization (WHO) 2008 classification of lymphoid malignancies.[23] Clinical information for all patients was collected in an anonymized database. The survival status and the cause of death were determined at the cut-off date of April 1, 2015. For staging, the Ann Arbor system was used for all patients, with the exception of those with cutaneous lymphomas, for whom the Mycosis Fungoides Cooperative Group (MFCG) tumor-node-metastasis (TNM) staging system of cutaneous T-NHL was used.[24] Statistical analyses of the data were performed using SPSS (version 23.0 for Windows).

A search in PubMed was performed to find additional cases of T-NHL in patients with varying causes of immunodeficiency using the following search terms: "Immunocompromised", "immunodeficiency", "decreased immunity", "reduced immunity", "HIV", "autoimmune disease", "rheumatoid arthritis", "IBD", "inflammatory bowel disease", "Crohn", "ulcerative colitis", "hematologic malignancy", "Hodgkin", "Waldenström", "B-cell lymphoma", "B-cell lymphoma", and "leukemia". These terms were combined using the "AND"-function with the search terms: "T-NHL", "T-cell lymphoma", "peripheral T-NHL", "peripheral T-cell lymphoma" or "PTCL". When available, Medical Subject Headings (MeSH) terms were used. In order to be included in the review herein, the cases of patients were required to have a pre-existing immunodeficiency due to HIV, immunosuppressive therapy, hematologic malignancies or a primary immunodeficiency before they developed a T-NHL. Reference lists of selected articles were used to identify additional articles. Articles published in a language other than English were excluded. Articles using earlier published cases were checked and duplicate cases were eliminated. Since more comprehensive reviews describing case series and previously published cases are available in the literature for T-NHL occurring in solid organ transplant recipients or in HIV patients, only these papers were included.

Results

Patients' characteristics

A total of 251 T-NHL cases were found in our histopathological database. Forty-two cases, for which no

continued from the previuos page

Extranodal sites	BM/Bone: 4 Skin: 4 Liver: 4 Nasopharynx: 1 Bowel: 1 Lung: 1 Heart: 1 Pancreas: 1 PCO:1	BM/Bone: 2 Skin: 1 Liver: 1 PB: 1 Spleen: 2 Lung: 1	BM/Bone: 1 Bowel: 2 Heart: 1 CZS: 1	Lung: 1	BM/Bone: 7 (28%) Skin: 5 (20%) Liver: 5 (20%) Spleen: 3 (12%) Bowel: 3 (12%) Lung:3 (12%) Heart: 2 (8%) Pancreas: 2 (8%) PB:1 (4%) PCO: 1 (4%) CZS: 1 (4%)
Stage*					
I/II	7 (50%)	1 (16.7%)	–	1 (100%)	9 (36%)
III/IV	7 (50%)	5 (83.3%)	4 (100%)	–	16 (64%)
Median survival (m)	62	7.2	8	96	11.3

*For cutaneous lymphomas the TNMB system was used. All other lymphomas were staged by the Ann Arbor staging system. AI: autoimmune; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma; B-CLL: B-cell chronic lymphatic leukemia; BM: bone marrow; CT: chemotherapy; CD: Crohn's disease; Dx: diagnosis; CTCL: primary cutaneous T-cell lymphoma; EN: extranodal; ENKL: extranodal NK/T cell lymphoma; HIV: human immunodeficiency virus; HSTCL: hepatosplenic T-cell lymphoma; IS(T): immunosuppressive (therapy); LN: lymphnodes involved; MCL: mantle cell lymphoma; MM: multiple myeloma; NR: not recorded/retraceable; PB: peripheral blood; PCO: pelvic cavity organs; PR: polymyalgia rheumatica; Prec T-LBL: precursor T-cell lymphoblastic lymphoma; Prim. C-CD30+ T-LPD: primary cutaneous CD30+ T-cell lymphoproliferative disease; PSC: primary sclerosing cholangitis; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; RA: rheumatoid arthritis; T-NHL: T-cell non-Hodgkin lymphoma; T-PLL; T-cell prolymphocytic leukemia; Tx: transplantation.

clinical data were available, were excluded (see flowchart, Figure 1). Twenty-five of the remaining 209 cases (12%) were identified in patients with an immunodeficiency. Table 1 and Table 2 give an overview of the clinical characteristics, ordered by the underlying disorder in the latter. The majority of cases of T-NHL were found in patients with an auto-immune disease (56%). Other underlying disorders were hematologic malignancies (24%), solid organ transplantation (16%) and HIV infection (4%). Previously published case reports and case series are summarized in *Online Supplementary Table S1,* also ordered by the underlying disorder. For comparison, in our PubMed search 605 cases of immunodeficiency-related T-NHL were identified, of which 201 occurred in patients with HIV infection (33%), 197 in transplant recipients (33%), 143 in patients with underlying autoimmune diseases (24%), 55 following previously treated hematologic malignancies (9%) and nine in patients with a primary immunodeficiency (1%).

In our series, T-NHL occurred at a median age of 52 years (interquartile range 39.5-73), which is nine to ten years younger than that observed in studies on T-NHL in the general population.[25,26] Patients with Crohn's disease and HIV were younger than patients with hematologic malignancies and solid organ transplantations. This is consistent with the literature on HIV and PTLD, in which the mean/median ages reported were 38-39 and 43.5-57.5 respectively.[14,15,17-20]

In line with these studies, we found a male predominance (80%).[14,15,17-20,26,27] Most patients had been treated with either immunosuppressive therapy or chemotherapy prior to the diagnosis of lymphoma (88%). For patients for whom information was available regarding the exact start date of the therapy with immunosuppressive or chemotherapeutic agents, the median interval between the start of the immunosuppressive treatment and the time of diagnosis was 76 months (interquartile range 14.3-171; N=16). In all patients for whom the duration of the drug use could be deduced from the clinical records, 60% had used one or more immunosuppressive or chemotherapeutic agents for at least two years (N=20). In all 25 patients, most (60%) had used prednisolone for varying periods. Azathioprine was used by 32%, including 86% of the patients with Crohn's disease; those for whom it was documented (7 out of 8) used this drug for longer than two years. Drugs somewhat less frequently used were chlorambucil and cyclophosphamide (both 16%), mostly by patients with hematologic malignancies, and tacrolimus (12%) by solid organ transplant recipients. A few patients had been treated with adalimumab, infliximab, rituximab,

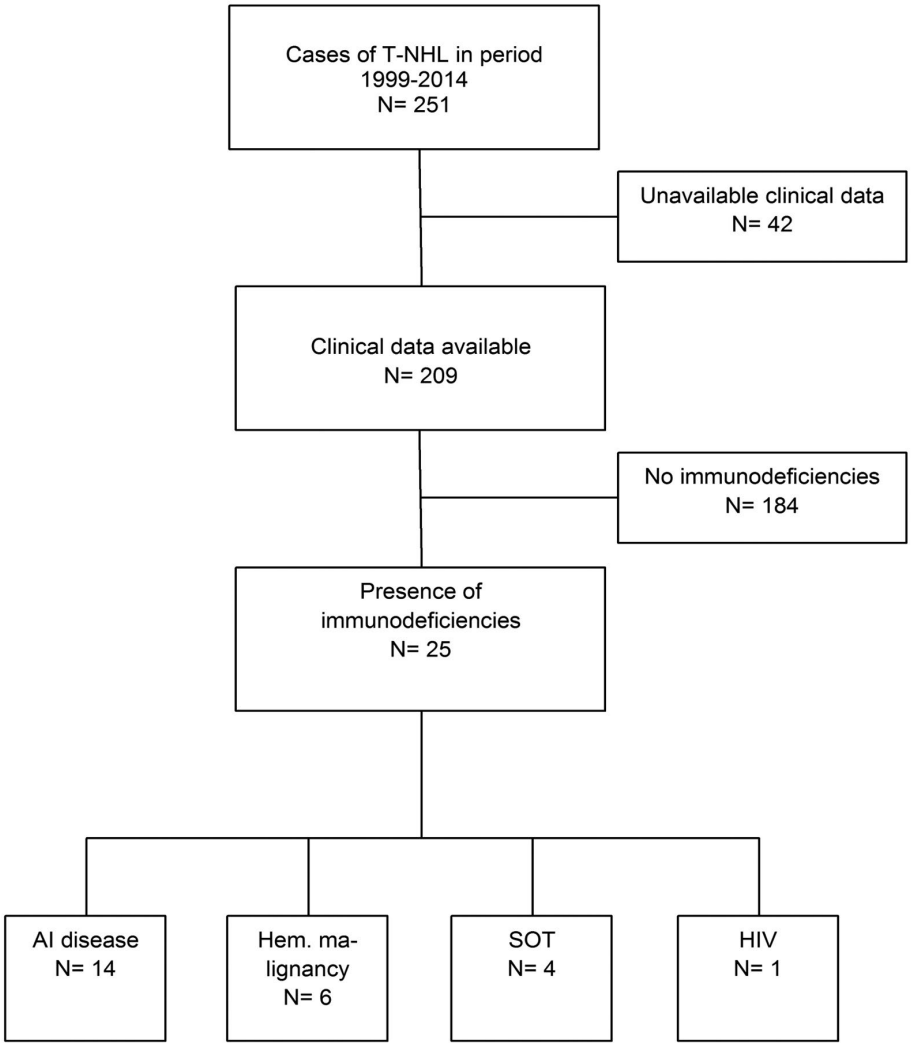

Figure 1. Cases included. Flowchart of inclusion of cases of T-NHL in patients with immunodeficiencies due to an underlying disorder or immunosuppressive drugs in the period 1999-2014. AI: autoimmune; Hem. malignancy: hematologic malignancy; HIV: human immunodeficiency virus; SOT: solid organ transplantation; T-NHL: T-cell non-Hodgkin lymphoma.

mycophenolate mofetil or sodium, a phosphatidylinositol 3-kinase (PI3K) inhibitor or pegylated interferon (PEG-INF).

In the cases reported in the literature, the use of thiopurines was also widespread (63% of all patients with autoimmune diseases and 86% of patients with IBD) (Table 3). TNF-α inhibitors like adalimumab, infliximab and etanercept were, in contrast to our series, the most frequently used drugs in patients with autoimmune diseases; 86% was treated a TNF-α inhibitor, often in combination with thiopurines (63% of this group). In the case reports concerning hematologic malignancies most patients were treated with a chemotherapeutic regime containing multiple agents (56%) and a few with chlorambucil only (6%) (Table 3).

Lymphoma characteristics

An overview of the histological characteristics of the lymphomas of our patients and those reported in the literature is provided in Table 2 and Table 4, respectively. T-NHL were morphologically and immunophenotypically highly variable. In our series, peripheral T-NHL (PTCL-NOS), was seen most frequently (24%), followed by anaplastic lymphoma kinase (ALK)-negative T-cell anaplastic large cell lymphomas (ALCL) (16%). There were three cases (12%) of angioimmunoblastic T-NHL (AITL), limited to the group of patients with autoimmune diseases. We saw only one case of HSTCL. This distribution was comparable to that in the general European population.[26] However, between the subtype distribution in the reported cases and that in the general population there were some differences. Most notable were the high frequency of primary cutaneous T-NHL in the immunocompromised patients (29% *vs.* 1.7%), a more frequent occurrence of HSTCL (12% *vs.* 1.4%), and the relative lack of AITL cases (1% *vs.* 18.5%) in this group.[26]

There was no predominance of either $CD4^+$ or $CD8^+$ lymphomas. Of the 19 cases in which CD4/CD8 staining had been carried out, seven (36.8%) were $CD8^+$, six (31.6%) were $CD4^+$, three (15.8%) were $CD4^+CD8^+$, and three cases (15.8%) were $CD4^-CD8^-$. EBER was performed in 23 lymphoma cases and the majority was negative (91.3%). EBER was positive in two cases (8.7%), one of which concerned extranodal natural killer (NK)/T-cell lymphoma and the other involving PTCL-NOS with EBV-positive T cells and concurrent EBV-positive B-cell blasts. In two other cases, both AITL, the malignant T cells were negative, but the B-cell compartment was EBV-positive. Figure 2 shows an example of a PTCL-NOS in a patient with B-cell chronic lymphocytic leukemia (B-CLL) as the underlying disorder.

Extranodal involvement was observed in the vast majority of patients (92%), and 16 patients (64%) showed an exclusively extranodal localization of the lymphoma. The most commonly involved organs were the bone marrow or bone, skin, liver, spleen, small bowel and lung. The heart, pancreas, peripheral blood, pelvic cavity organs and central nervous system were affected in some cases (Table 2). This rate of extranodal involvement is higher than the 65-72% which has been reported in the general, immunocompetent population,[25,28] and is consistent with more frequently occurring extranodal localizations of B-cell lymphomas in patients with either primary or acquired immunodeficiencies.[3,17,29-31]

The majority of patients had Ann Arbor stage III/IV disease at presentation (64%). The four patients staged according to the MFCG TNM staging system of cutaneous T-cell lymphomas had stage I or II disease.

Treatment and outcome

As shown in Table 5, in our series lymphoma treatment was very heterogeneous due to the different histological subtypes and clinical stages of disease.

After a median follow-up of six years, 15 patients had died. The median overall survival (OS) was 11.3 months (table 2) and the 1- and 5-year survival rates were 47% (95% confidence interval (CI) 27-67%) and 31% (95% CI 7-55%), respectively. This is somewhat lower than the 5-year survival rate reported in patients with T-NHL in the general population (38-49%),[25,28,32] and consistent with a worse survival of HIV and post-transplant patients with T-NHL.[14,15,17-19] Since worse outcomes have been reported for certain histological subtypes as compared to others,[25,26,28] outcomes were calculated separately for the total number of patients with PTCL-NOS, AITL and HSTCL (n=10). The median OS in this group was 7.5 months with a 5-year survival rate of 20% (95% CI -6-46%), which is indeed lower than the median OS of 60 months and the 5-year survival rate of 41% (95% CI 8-74%) in patients with the remaining histological subtypes.

Twelve of the 15 deceased patients died within four months following diagnosis. The main causes of death, in

Table 3. Use of drugs in cases reported in the literature.

AID		Nr pts	TNF-αi	Thiop	TNF-αi + thiop	MTX	CsA	Other
	IBD	64	60	55	48	2	–	–
	Other AID	79	63	35	30	11	6	5
	Total	143	123	90	78	13	6	5
HM		Nr pts	CT	CA only	Melfalan	None	NR	
	CLL	44	20	3	–	13	8	
	Other HM	11	9	–	1	1	–	
	Total	55	29	3	1	14	8	
Other ID		None						
		9						

AID: autoimmune disease; CA: chlorambucil; CLL: chronic lymphocytic leukemia; CsA: cyclosporine A; CT: chemotherapy, multiple agents; HM: hematologic malignancies; IBD: inflammatory bowel disease; ID: immunodeficiencies ; MTX: methotrexate; Nr pts: number of patients; Thiop: thiopurines; TNF-αi: TNF-α inhibitors.

Table 4. Distribution of histologic subtypes in cases reported in the literature.

	HIV	Post tx	AID	HM	Other ID	Total
ALCL	52	16	12	3	1	84
ALK+	2	4	2	2		10
ALK –	27		3	1	1	32
ALK NR	23	12	7			42
AITL	2		3	1		6
ATLL	11	6				17
CTCL	48	48	34	39	4	173
EATL		1				1
ENKL	1	8	3		1	13
HSTCL	1	23	47	1	1	73
IVL		1				1
NKL		6				6
NKTCL	10	4				14
Prec T-LBL		8				8
PTCL, NOS	76	53	5	10	2	146
SPTCL		3	5	1		9
T-LGL		9				9
Other T-NHL		11	34			45
Total	201	197	143	55	9	605

AID: autoimmune disease; AITL: angioimmunoblastic T-cell lymphoma; ALCL: anaplastic large cell lymphoma, systemic; ALK: anaplastic lymphoma kinase; ATLL: adult T-cell leukemia/lymphoma; CTCL: primary cutaneous T-cell lymphoma; EATL: enteropathy-associated T-cell lymphoma; ENKL: extranodal NK/T-cell lymphoma; HM: hematologic malignancies; HSTCL: hepatosplenic T-cell lymphoma; ID: immunodeficiency; IVL: intravascular lymphoma; NKL: natural killer cell lymphoma(/leukemia); NKTCL: natural killer/T-cell lymphoma; NR: Not recorded or not known; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; Prec T-LBL: precursor T-cell lymphoblastic lymphoma; SPTCL: subcutaneous panniculitis-like T-cell lymphoma; T-LGL: T-cell large granular lymphocytic leukemia; T-NHL: T-cell non-Hodgkin lymphoma; tx: transplantation.

those cases for which this information was available, were lymphoma progression (N=6) or sepsis (N=2). One patient developed two other malignancies and the exact cause of death remained unknown.

Discussion

In the general population, T-cell neoplasms are uncommon, representing about 5 to 10% of all NHL in Western countries.[26] While B-cell lymphomas are known to occur more frequently in transplant recipients and in patients with IBD, HIV or autoimmune diseases,[3,5,6,11] for T-NHL this data has not been elucidated as of yet. Since T-NHL are tumors of the immune system, akin to B-cell lymphomas, it is likely that the risk of developing a T-NHL is also increased in patients with an impaired immune system. However, a higher incidence of T-NHL has only been reported for a few specific patient groups, including HIV patients,[14,15] solid organ transplant recipients[19] and patients with a history of coeliac disease, psoriasis or eczema.[33,34] Furthermore, a higher incidence of the rare hepatosplenic T-NHL has been documented in IBD patients on thiopurines.[21]

The present study of 25 patients is the largest case series of T-NHL in patients with varying causes of acquired immunodeficiencies published thus far. These 25 patients, diagnosed at our center between 1999 and 2014, constitute 12% of the total number of cases of T-NHL in which clinical data were available. Three of these 25 patients developed AITL, which may be accompanied by autoimmune features such as arthritis and synovitis, and can therefore resemble RA.[35] The autoimmune diseases in these three patients were RA, polymyalgia rheumatica and sarcoidosis, which had been diagnosed 30 years, five years and three years, respectively, prior to the diagnosis of AITL. These lengthy intervals signify that it is most unlikely that they were manifestations of the AITL itself, since arthritis occurring more than six months in advance of the diagnosis is extremely uncommon.[35]

To determine whether T-NHL occurs more often in immunocompromised patients than in the general population, the prevalence of patients with an immunodeficiency within the cohort of patients with T-NHL should be compared to the prevalence of patients with an immunodeficiency in the general population. Since no data are available on the overall prevalence of immunodeficiencies in the general population, we compared the frequencies of specific underlying disorders in the Dutch context. We did this for IBD, B-CLL and RA, the three most consistent underlying disorders which we witnessed, apart from solid organ transplantation for which an association with the occurrence of T-NHL is already known.[17,19,30] Based on a prevalence of IBD in 432 patients per 100,000 inhabitants in 2010,[36] we would expect that 0.90 of the 209 T-NHL would occur in patients with IBD, compared to the seven we actually found. For B-CLL, a prevalence of 5,061 patients (average number in 2013/2014)[37] out of a total population of 16,829,289[38] leads to an expectation of 0.063 patients with B-CLL in our cohort, within which we identified an actual number of four patients. A similar calculation for RA, which had a prevalence of 116,000 patients in

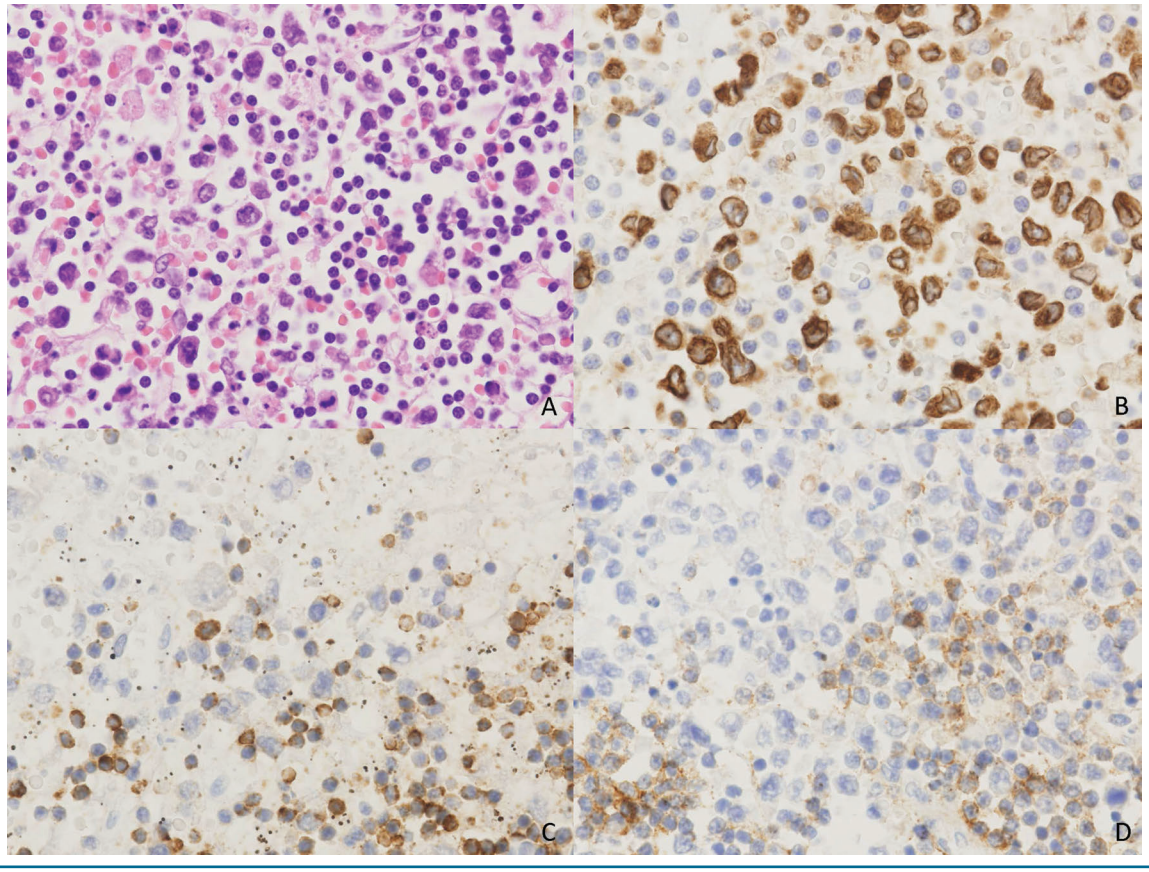

Figure 2 . The hematoxylin and eosin stain shows large atypical cells in a background of small monomorphic lymphocytes. (A) The large atypical cells are positive for CD3 (B) and show loss of expression of CD5. (C) The small lymphocytes in the background are B-cells (CD20) with co-expression of CD5 (D), consistent with residual B-CLL in the background of this T-cell lymphoma.

2011[39] out of a population of 16,574,989[38] leads to an expected number of 1.46 compared to an actual number of 3 patients. The numbers of expected cases for IBD and RA are probably overestimated, since the prevalence of IBD and RA in the general population that we used for these calculations also included all non-treated patients, who were excluded in our case series. Regarding RA, it is known that only about 10% of the patients with this disease who are registered are treated by a rheumatologist or other medical specialist, which generally corresponds with the use of immunosuppressive drugs.[39] Using this information, when we recalculated the expected number of patients with RA in our cohort, we found a number of only 0.146 compared to the actual number of three. The probability of observing a certain number of cases, given an expected number of cases, can be calculated *via* the Poisson distribution. By using this method, we found a probability of 4.34E-05 that at least seven cases of IBD would occur given an expected number of 0.90. The probability of at least four cases of B-CLL compared to an expected number of 0.063 is 6.24E-07. For RA the probability of three cases occurring is 0.00047 when the expected number is 0.146. These calculations, even when bearing in mind the referral bias of our center, suggest that for B-CLL patients and those on immunosuppressive drugs for the treatment of IBD and RA, the risk of developing a T-NHL is higher than in the general population.

Taking into account the additional 596 cases we found in the literature of T-NHL in patients with impaired immunity due to HIV, hematologic malignancies and immunosuppressive drugs, this observation might be extrapolated to all patients with secondary immunodeficiencies. Whether patients with primary immunodeficiencies are also at risk for developing T-NHL is less clear, since we found only nine such cases in the literature. In this particular group of patients polyclonal T-cell proliferations are seen more often than overt T-cell lymphomas.[8]

The pathogenesis of T-NHL in immunodeficient patients is unclear. In our series the majority of lymphomas were EBV-negative, suggesting that, in contrast to B-cell lymphoproliferative disorders in immunocompromised patients, EBV does not play a role in this setting. Infection by other viruses, such as human T-lymphotropic virus type 1 (HTLV1) and human herpes virus (HHV)-6, possibly plays a role in development, as is suggested for T-cell PTLD.[40-42] Another possible mechanism is that immune dysfunction contributes to lymphomagenesis by diminished immunosurveillance when malignant mutations arise in lymphoid cells due to other causes, for instance chronic antigenic stimulation or environmental factors, including mutagenic effects of chemotherapeutic or immunosuppressive drugs.[42,43] Furthermore, a common biological basis of the first and second malignancy in hematologic malignancies has been suggested, ie., due to

malignant transformation of a stem cell with the capacity to differentiate in either a B- or a T-NHL or a shared genetic predisposition for the two lymphomas.[44,45] An example of this is the ten-eleven translocation 2 (*TET2*) mutation. *TET2* is a dioxygenase that plays an important role in hematopoietic stem cells and progenitor cells by catalyzing multiple steps of 5-methylcytosine oxidation. *TET2* mutations are commonly found in myeloid cancers, in

Table 5. Treatment and outcome.

Histological Subtype	First-line therapy	R	Second-line therapy	R	OC	S (m)	Cause of death
PTCL, NOS	None, confirmation diagnosis after death				Death	0	Sepsis (mycobacterial infection)
PTCL, NOS	None, palliative treatment			Death	<1		Rapid progression
PTCL, NOS	None, diagnosis at autopsy			Death	0		MOF and ARDS, high lymphoma load
PTCL, NOS	Cytarabine, idarubicine	PR	DHAP-VIM-DHAP	PD	Death	4	Refractory disease
PTCL, NOS	CHOEP, autologous SCT and HD-MTX		CR			Alive	19
PTCL, NOS	CHOP, alemtuzumab	CR			Alive	111	
ALCL ALK-	None, palliative treatment			Death	<1		Rapid progression
ALCL ALK-	CHOP and intrathecal MTX	CR, relapse	DHAP	CR	Alive	102	
ALCL ALK-	CHOP	PD	DHAP; third line: brentuximab; fourth line: Cyclophosphamide, fludarabine, TBI, followed by allo-CB SCT		CR	Alive	21
ALCL ALK-	Reversed CHOP				Death	1	Sepsis caused by bowel perforation due to lymphoma
ALCL ALK+	Cyclofosfamide, doxorubicine, prednisolone	CR, relapse	DHAP; third line: VIM	SD	Death	41	NR, besides lymphoma also gallbladder cancer and HCC
AITL	CHOP	PR			Death	3	Chemotherapy complications
AITL	CHOP	SD	DHAP-VIM-DHAP + alemtuzumab	SD	Death	9	NR
AITL	Prednisolone	NR			Death	4	NR
MF	PUVA, topical steroids, MTX, prednisolone	PD	RT	PR	Death	61	NR
MF	PUVA, topical steroids	CR			Alive	65	
Prim. C-CD30$^+$ T-LPD	No treatment, self-limiting	CR			Alive	74	
Prim. C-CD30$^+$ T-LPD	RT	CR, relapse	RT	CR	Alive	69	
Precursor T-LBL	Multiple chemotherapeutic agents (HOVON-70-protocol)	CR			Alive	76	
Precursor T-LBL	Prednisolone, vincristin, daunorubicin, PEG-asparaginase and intrathecal MTX	CR			Alive	8	
ENKL, nasal type	CHOP	CR			Alive	49	
HSTCL	NR, treatment in other center	NR			Death	3	NR
T-PLL	Prednisolone	NR			Death	4	NR
Liquor/CNS	RT				Death	1	Rapid progression
T-NHL, unclass.	None, palliative treatment				Death	1	Rapid progression

AITL: angioimmunoblastic T-cell lymphoma; ALCL: T-cell anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; ARDS: acute respiratory distress syndrome; CB SCT: cord blood stem cell transplantation; CHOEP: cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone; CR: complete remission; DHAP: dexamethasone, high dose cytarabine and cisplatinum; ENKL: extranodal NK/T-cell lymphoma; HSTCL: hepatosplenic T-cell lymphoma; LTF: lost to follow-up; MF: mycosis fungoides; MOF: multi-organ failure; MTX: methotrexate; NR: not recorded or not known; OC: outcome; PD: progressive disease; PR partial remission; Prim. C-CD30$^+$ T-LPD: primary cutaneous CD30$^+$ T-cell lymphoproliferative disease; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; PUVA: psoralen plus ultraviolet A; R: response; RT: radiotherapy; S: survival; SD: stable disease; T-LBL: T-cell lymphoblastic lymphoma; T-PLL: T-cell prolymphocytic leukemia; TBI: total body irradiation; VIM: ifosfamide, mitoxantrone and etoposide.

about 11.9 % of all T-NHL, particularly in AITL and PTCL, in NOS, and in about 2% of B-NHL. The same *TET2* mutations, for example, have been found in patients with AML/MDS secondary to a previous lymphoma, suggesting a shared genetic origin.[46,47] Moreover, it has been observed that *TET2* loss in mice leads to hypermutagenicity in hematopoietic stem cells and progenitor cells, resulting in an increased risk of various hematologic malignancies.[48]

Considering that most patients had been treated with immunosuppressive drugs or chemotherapy for intervals of longer than two years, it seems that prolonged treatment with these types of drugs increases the risk of malignant lymphoma development. An association between the use of thiopurines alone or combined with TNF-α inhibitors and the development of HSTCL in IBD patients has been reported previously.[15] The majority of patients with IBD in our series and in the reported cases had been using azathioprine. It is possible, therefore, that the use of thiopurines also contributes to the development of other T-NHL.

Obviously, inherent to its retrospective design, our study has some limitations. The clinical data were not complete for all patients, thus making it difficult to assess the temporal relationship between the underlying disorders or drug use and the development of T-NHL for some. In addition, the group was too small to run subgroup analyses. Moreover, since the overall prevalence of immunodeficiencies in the general population is not known, we could only compare the prevalence of specific underlying disorders in our cohort of patients with T-NHL to those in the general population.

Conclusion

The 25 cases presented herein, together with the 596 cases found in the literature of T-NHL in patients with varying causes of immunodeficiencies suggest that patients with a secondary immunodeficiency are at increased risk for the development of T-NHL. Prolonged treatment with immunosuppressive or chemotherapeutic drugs seems to contribute to the risk. T-NHL in immunodeficient patients are histologically very heterogeneous. The distribution of subtypes resembles that present in the general population, with the exception of primary cutaneous T-NHL and HSTCL, both of which have been reported more often in patients with an immunodeficiency, and AITL, which has been reported less frequently in this group. Overall, the prognosis seems worse compared to T-NHL of similar subtypes in the general population. T-NHL occur predominantly in men, and in immunodeficient patients they tend to be more often located extranodally, which is in line with B-cell lymphomas in this group of patients. In our series of immunodeficient patients, the lymphomas occurred on average nine to ten years earlier than T-NHL in the general population.

The observations in the study herein should raise awareness of the possible development of T-NHL in immunodeficient patients and challenge the prolonged use of immunosuppressive drugs in patients who are in clinical remission of their autoimmune disease.

Funding

The study was supported by Lymph&Co and by a grant from the Egbers Foundation.

References

1. Gatti RA, Good RA. Occurrence of malignancy in immunodeficiency diseases. A literature review. Cancer. 1971;28(1):89-98.
2. Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant lymphomas in transplantation patients. Transplant Proc. 1969;1(1):106-112.
3. Parker A, Bowles K, Bradley JA, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. Br J Haematol. 2010;149(5):675-692.
4. Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non-Hodgkin lymphoma. Lancet. 1991;337(8745):805-809.
5. Levine AM, Seneviratne L, Espina BM, et al. Evolving characteristics of AIDS-related lymphoma. Blood. 2000;96(13):4084-4090.
6. Bewtra M. Lymphoma in inflammatory bowel disease and treatment decisions. Am J Gastroenterol. 2012;107(7):964-970.
7. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374(9701):1617-1625.
8. Gratzinger D, Jaffe ES, Chadburn A, et al. Primary/congenital immunodeficiency: 2015 SH/EAHP workshop report-part 5. Am J Clin Pathol. 2017;147(2):204-216.
9. Simon TA, Thompson A, Gandhi KK, Hochberg MC, Suissa S. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. Arthritis Res Ther. 2015;17:212.
10. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004;50(6):1740-1751.
11. Zintzaras E, Voulgarelis M, Moutsopoulos HM. The risk of lymphoma development in autoimmune diseases: a meta-analysis. Arch Intern Med. 2005;165(20):2337-2344.
12. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. 2005;64(10):1414-1420.
13. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006;54(3):692-701.
14. Castillo JJ, Beltran BE, Bibas M, et al. Prognostic factors in patients with HIV-associated peripheral T-cell lymphoma: a multicenter study. Am J Hematol. 2011;86(3):256-261.
15. Gilardin L, Copie-Bergman C, Galicier L, et al. Peripheral T-cell lymphoma in HIV-infected patients: a study of 17 cases in the combination antiretroviral therapy era. Br J Haematol. 2013;161(6):843-851.
16. Biggar RJ, Engels EA, Frisch M, Goedert JJ. Risk of T-cell lymphomas in persons with AIDS. J Acquir Immune Defic Syndr. 2001;26(4):371-376.
17. Herreman A, Dierickx D, Morscio J, et al. Clinicopathological characteristics of post-transplant lymphoproliferative disorders of T-cell origin: single-center series of nine cases and meta-analysis of 147 reported cases. Leuk Lymphoma. 2013;54(10):2190-2199.
18. Perez K, Castillo J, Dezube BJ, Pantanowitz L. Human immunodeficiency virus-associated anaplastic large cell lymphoma. Leuk Lymphoma. 2010;51(3):430-438.
19. Swerdlow SH. T-cell and NK-cell post-transplantation lymphoproliferative disorders. Am J Clin Pathol. 2007;127(6):887-895.
20. Seckin D, Barete S, Euvrard S, et al. Primary cutaneous posttransplant lymphoproliferative disorders in solid organ transplant recipients: a multicenter European case series. Am J Transplant. 2013;13(8):2146-2153.
21. Deepak P, Sifuentes H, Sherid M, Stobaugh D, Sadozai Y, Ehrenpreis ED. T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-alpha) inhibitors: results of the REFURBISH study. Am J Gastroenterol. 2013;108(1):99-105.
22. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol.

2011;9(1):36-41 e1.
23. Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues (4th ed). Lyon, France: International Agency for Research on Cancer. 2008.
24. Olsen E, Vonderheid E, Pimpinelli N, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007;110(6):1713-1722.
25. Lopez-Guillermo A, Cid J, Salar A, et al. Peripheral T-cell lymphomas: initial features, natural history, and prognostic factors in a series of 174 patients diagnosed according to the R.E.A.L. Classification. Ann Oncol. 1998;9(8):849-855.
26. Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008;26(25):4124-4130.
27. Jaffe ES, Harris NL, Stein H, Isaacson PG. Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. Blood. 2008;112(12):4384-4399.
28. Arrowsmith ER, Macon WR, Kinney MC, et al. Peripheral T-cell lymphomas: clinical features and prognostic factors of 92 cases defined by the revised European American lymphoma classification. Leuk Lymphoma. 2003;44(2):241-249.
29. Ferreri AJ. Risk of CNS dissemination in extranodal lymphomas. Lancet Oncol. 2014;15(4):e159-169.
30. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas. Ann Oncol. 1997;8(8):727-737.
31. Tran H, Nourse J, Hall S, Green M, Griffiths L, Gandhi MK. Immunodeficiency-associated lymphomas. Blood Rev. 2008;22(5):261-281.
32. Gisselbrecht C, Gaulard P, Lepage E, et al. Prognostic significance of T-cell phenotype in aggressive non-Hodgkin's lymphomas. Groupe d'Etudes des Lymphomes de l'Adulte (GELA). Blood. 1998;92(1):76-82.
33. Ekstrom Smedby K, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. Blood. 2008;111(8):4029-4038.
34. Wang SS, Flowers CR, Kadin ME, et al. Medical history, lifestyle, family history, and occupational risk factors for peripheral T-cell lymphomas: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr. 2014;2014(48):66-75.
35. Tsochatzis E, Vassilopoulos D, Deutsch M, Filiotou A, Tasidou A, Archimandritis AJ. Angioimmunoblastic T-cell lymphoma-associated arthritis: case report and literature review. J Clin Rheumatol. 2005;11(6):326-328.
36. De Groof J, Rossen N, van Rhijn B, et al. P644 Epidemiology and characteristics of inflammatory bowel disease in a large population-based cohort in the Netherlands. Poster presentations European Crohn's and Colitis Organisation, 2015.
37. The Netherlands Cancer Registry.
38. Statistics Netherlands (CBS).
39. National Institute of Public Health and the Environment (RIVM).
40. Hoshida Y, Li T, Dong Z, et al. Lymphoproliferative disorders in renal transplant patients in Japan. Int J Cancer. 2001;91(6):869-875.
41. Lin WC, Moore JO, Mann KP, Traweek ST, Smith C. Post transplant CD8+ gammadelta T-cell lymphoma associated with human herpes virus-6 infection. Leuk Lymphoma. 1999;33(3-4):377-384.
42. Fisher SG, Fisher RI. The epidemiology of non-Hodgkin's lymphoma. Oncogene. 2004;23(38):6524-6534.
43. Barzilai A, Trau H, David M, et al. Mycosis fungoides associated with B-cell malignancies. Br J Dermatol. 2006;155(2):379-386.
44. Campidelli C, Sabattini E, Piccioli M, et al. Simultaneous occurrence of peripheral T-cell lymphoma unspecified and B-cell small lymphocytic lymphoma. Report of 2 cases. Hum Pathol. 2007;38(5):787-792.
45. Herro E, Dicaudo DJ, Davis MD, Weaver AL, Swanson DL. Review of contemporaneous mycosis fungoides and B-cell malignancy at Mayo Clinic. J Am Acad Dermatol. 2009;61(2):271-275.
46. Ko M, An J, Pastor WA, Koralov SB, Rajewsky K, Rao A. TET proteins and 5-methylcytosine oxidation in hematological cancers. Immunol Rev. 2015;263(1):6-21.
47. Solary E, Bernard OA, Tefferi A, Fuks F, Vainchenker W. The Ten-Eleven Translocation-2 (TET2) gene in hematopoiesis and hematopoietic diseases. Leukemia. 2014;28(3):485-496.
48. Pan F, Wingo TS, Zhao Z, et al. Tet2 loss leads to hypermutagenicity in haematopoietic stem/progenitor cells. Nat Commun. 2017;8:15102.