

Table S1a. Clinical comparison between cHL and T-cell lymphomas.

	Age	Symptoms	Localization	BM Involvement	Prognosis	Treatment
cHL	Younger Middle age	B-Symptoms	Typical: lymph nodes Other: mediastinum	Unusual	Good	ABVD; RT
ALK+ALCL	Children Young adults	Severe systemic symptoms	Lymph nodes; skin; bone; soft tissues	Usual	Good	CHOP-like
ALK-ALCL	Adults	B-Symptoms	Lymph nodes; skin; liver; lung	Unusual	Often relaps	CHOP
BIA-ALCL	8-10 years after breast implant	Local mass/seroma	Breast	Unusual	Indolent	Surgical excision
AITL	Elderly	Ascites; skin rash; autoimmune-like manifestations	Lymph nodes Visceral organs	Usual	Poor	Not established
F-PTCL	None	As AITL	As AITL; inguinal lymph nodes	Usual	Poor	Not established

Table S1b. Morphologic comparison between cHL and T-cell lymphomas.

	Growth Pattern	Neoplastic Component	Background	Morphological Hallmark	Genetic Hallmark
cHL	Frequently nodular	RSC	Lymphocytes, histiocytes,granulocytes	Isolate RSCs in appropriate background	none
ALK+ALCL	Common pattern: diffuse/infiltrative In Hodgkin-like pattern: nodular	Large T-cells CD30+ ALK+	Common pattern: isolate lymphocytes Hodgkin-like pattern: polymorphous infiltrate	Clusters of large CD30+/ ALK+ cells; horse-shoe shaped nuclei	ALK gene rearrangement
ALK-ALCL	Diffuse/infiltrative	Large T-cells CD30+ ALK-	Sclerosis and eosinophilia	As ALK+ ALCL	none
BIA-ALCL	Diffuse	Medium-to large-sized T- cells	Fibrinoid material and necrosis; inflammatory infiltrate	Non-cohesive sheets of malignant cells	none
AITL	Diffuse with capsular/perinodal infiltration	Small-to medium-sized T cells clustering close to vessels	Histiocytes, RSLCs (immunoblasts), eosinophils, plasma cells	Marked proliferation of arborizing high endothelial venules	none
F-PTCL	Follicular-like progressive transformation of germinal center	Small-to medium-sized T- cells	None	Follicles involved	none

Table S1c. Immunohistochemical comparison between cHL and T-cell lymphomas.

	RSC in cHL	RSLC in ALK+ALCL	RSLC in ALK-ALCL	RSLC in BIA-ALCL	RSLC in AITL	RSLC in F-PTCL
B-markers	Negative. CD20 weak <20%	Negative	Negative	Negative	CD20+; CD79alfa+	CD20+ (32%)
T-markers	Negative	CD2+, CD4+, CD5+	Negative GranzymeB+, CD43+	Incomplete T-cell phenotype/CD4+/NK	Negative	Negative
CD30	Positive	Positive	Positive	Positive	Positive	Positive
CD15	Positive	Rarely positive	Negative	Occasionally positive	Positive	Rarely positive
LMP1	Positive	Negative	Negative	Negative	Occasionally positive	Positive (47%)
PAX5	Positive (weak)	Negative	Negative	Occasionally positive	Positive	Positive (strong)
CD45	Negative	Variably positive	Positive	Positive	Positive	Positive
MUM1	Positive	Negative	Negative	Negative	Occasionally positive	Positive
EMA	Negative	Positive	Rarely positive	Positive (43-90%)	Negative	Negative
Hallmark	CD30+/CD15+	ALK+	Perforin+; CD56+; Clusterin+	TCR genes rearrangements	Background of T-cell CD10+, BCL6+; TRC gene rearrangements	Follicular proliferation of small lymphocytes expressing T-markers

Table S2a. Clinical comparison between cHL and High Grade B-cells Lymphomas.

	Age	Symptoms	Localization	BM Involvement	Prognosis	Treatment
cHL	Younger Middle age	B-Symptoms	Typical: lymph nodes Other: mediastinum	Unusual	Good	ABVD; RT
DLBCL, NOS	Elderly	B-Symptoms	Typical: lymph nodes Other: Gastro-Intestinal tract	10-20% Concordant (DLBCL) Discordant (Low Grade)	Variable (see in the text)	R-CHOP; autologous stem cell transplantation
THRLBCL	Middle	B-Symptoms; Hepatosplenomegaly	Lymph nodes	Common	Poor	R-CHOP
ALK+LBCL	All age	B-Symptoms	Typical: lymph nodes Other: Mediastinum	25-30%	Poor	CHOP
PMBL	35-37 y.o.	Mediastinic syndrome	Mediastinum Lymph nodes	Uncommon	Variable (see in the text)	Not established
GZL	<30 y.o.	Mediastinic syndrome	Mediastinum Lymph nodes	Uncommon	Poor	CHOP
LG	46-48 y.o. immunocompromised	Fever; cough	Lungs	Uncommon	Variable (see in the text)	Variable (see in the text)
PEL	40-45 y.o. Immunocompromised	Cavitary form: effusion; extracavitary form: mass related	Cavitary: pleural, pericardial, peritoneal.	Uncommon	Poor	Not established
EBV+DLBCL	Elderly	Organ-related	Visceral organs	Common	Poor	As DLBCL, NOS
MCL	66 y.o.	B-Symptoms	Lymph nodes Extranodal organs	Common	Poor	R-HyperCVAD R-MA

Table S2b. Morphologic comparison between cHL and High Grade B-cells Lymphomas.

	Growth Pattern	Neoplastic Component	Background	Morphological Hallmark	Genetic Hallmark
cHL	Nodular	RSC	Lymphocytes, histiocytes, granulocytes	Isolate RSCs in appropriate background	None
DLBCL, NOS	Diffuse	Large-to medium-sized B-cells	Small T-cells and histiocytes	Large-to medium-sized B cells effacing lymph node	None
THRLBCL	Diffuse	RSLC with B immunophenotype	Host T lymphocytes with/without epithelioid histiocytes	Host T lymphocytes with/without epithelioid histiocytes	None
ALK+LBCL	Diffuse or sinusoidal	Monomorphic B-cells ALK+	None	Plasmablastic like cells effacing lymph node	ALK gene rearrangement
PMBL	Diffuse	Medium-to large B-cells CD23+	Variable degree of sclerosis and collagen band.	Variable degree of sclerosis and collagen band.	None
GZL	Wide variation	B-cells with morphologic and immunophenotypic findings intermediate between cHL and DLBCL	Paucity of inflammatory cells	High tumor cell content	None
LG	Angiocentric and angiodestructive	EBV+ B cells	Occasional plasma cells; necrosis	Angiocentric and angiodestructive infiltrate	None
PEL	Isolate cells	HHV8+ large-sized B cells	None	HHV8+ large-sized B cells	None
EBV+DLBCL	Diffuse	EBV+ large-sized B cells	Numerous small lymphocytes and histiocytes and plasma cells	EBV+ large-size B cells	None
MCL	Nodular or diffuse	Cyclin D1+ small-to medium-sized B cells	None	Cyclin D1+ small-to medium size B cells	t(11-14)

Table S2c. Immunohistochemical comparison between cHL and High Grade B-cells Lymphomas.

	RSC in cHL	RSLC in DLBCL, NOS	RSLC in THRLBCL	RSLC in ALK+LBCL	RSLC in PMBL	RSLC in GZL	RSLC in LG	RSLC in PEL	RSLC in EBV+DLBCL	RSLC in MCL
B-markers	Negative. CD20 weak <20%	Positive, strong	Positive, strong	Negative	Positive, strong	Variable	Positive	Positive in extracavitary	Positive, strong	Positive
T-markers	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Aberrant	Negative	CD5+
CD30	Positive	Positive (10- 15%)	Usually negative	Usually negative	Usually positive, weak	Variable	Usually positive	Usually positive	Positive (30%)	Usually positive
CD15	Positive	Negative	Usually negative	Negative	Usually negative	Variable	Negative	Negative	Rarely positive	Variable
LMP1	Positive	Negative	Negative	Negative	Negative	Variable	Positive	Negative	Positive	Variable
PAX5	Positive, weak	Positive, strong	Positive	Negative	Positive, strong	Variable	Positive	Positive	Positive	Positive
CD45	Negative	Positive	Positive	Negative	Positive	Variable	Positive	Positive	Positive	Positive
MUM1	Positive	Negative	Negative	Positive	Positive	Variable	Variable	Positive	Positive	Negative
EMA	Negative	Negative	Positive (30%)	Positive (90%)	Negative	Variable	Negative	Usually positive	Usually negative	Negative
Hallmark	CD30+/CD15+ (BOB1- OCT2-)	BOB1+ and OCT2+	BCL6+	ALK+; BOB1+ and OCT2+	CD23+; BOB1+ OCT2+	None	None	HHV8+; BOB1+ and OCT2+	EBER+	CD5+; cyclinD1+ SOX11+

Table S3a. Clinical comparison between cHL and Low Grade B-cells Lymphomas.

	Age	Symptoms	Localization	BM Involvement	Prognosis	Treatment
cHL	Younger Middle age	B-Symptoms	Typical: lymph nodes Other: mediastinum	Unusual	Good	ABVD; RT
FL	60-65 y.o.	B-Symptoms	Cervical and Abdominal Lymph nodes	Usual	Good	Depending on stage (see in the text)
PCMZL	Young-to middle age	Solitary or grouped skin lesions	Skin	Very unusual	Good	Local skin-directed
CLL/SLL	Elderly	Lymphadenopathy	Lymph nodes	Usual	Good	Wait-and-see
pcFCL	Middle age to older	Skin lesions	Skin	5%	Good	Local skin-directed

Table S3b. Morphologic comparison between cHL and Low Grade B-cells Lymphomas.

	Growth Pattern	Neoplastic Component	Background	Morphological Hallmark	Genetic Hallmark
cHL	Nodular	RSC	Lymphocytes, histiocytes, granulocytes	Isolate RSCs in appropriate background	none
FL	Nodular; Diffuse; Mixed	Small-to medium-sized B-lymphocytes of Germinal Center	Reactive T-cells, FDCs and histiocytes	Nodular/Diffuse proliferation of small-to medium-sized lymphocytes	t(11;14)
PCMZL	Nodular/diffuse dermal infiltration	Small-to medium-sized 'marginal zone cells' and larger B-cells	Plasmacytoid lymphocytes, plasma cells, T-lymphocytes, histiocytes	Grenz zone without epidermotropism	None
CLL/SLL	Nodular	Monomorphic small B cells with scattered larger cells	Monomorphous lymphocytes proliferation	Proliferation centers	None
pcFCL	Nodular, diffuse, mixed	Medium-to large-sized centrocytes and immunoblasts	In follicular pattern: reactive small lymphocytes	Skin-restricted lesions	None

Table S3c. Immunohistochemical comparison between cHL and Low Grade B-cells Lymphomas.

	RSC	RSLC in FL	RSLC in PCMZL	RSLC in CLL/SLL (Type I)	RSLC in pcFCL
B-markers	Negative. CD20 weak <20%	Positive; CD10+, BCL6+, BCL2+	CD20+ strong and BCL2+	CD20 in 20-30%	CD20 strong
T-markers	Negative	Negative	Negative	Negative	Negative
CD30	Positive	Focal and weak	Positive	Positive	Positive
CD15	Positive	Negative	Negative	Positive	Negative
LMP1	Positive	Negative	Negative	Usually positive	Negative
PAX5	Positive, weak	Positive	Positive	Positive	Positive
CD45	Negative	Positive	Positive	Positive	Positive
MUM1	Positive	Negative	Negative	Negative	Positive
EMA	Negative	Negative	Negative	Negative	Negative
Hallmark	CD30+/CD15+	CD10+, BCL6+, BCL2+	Strong expression of B-markers	None	Strong expression of B-markers