

The background of the slide features a microscopic view of cells. Two large, prominent cells in the center have bright pink nuclei and blue, irregularly shaped cytoplasmic borders. Several other cells, mostly with pink nuclei, are visible in the periphery, some partially cut off by the frame. The overall color palette is dominated by pink, blue, and black.

Composite Lymphoma

Lymphoma Tumor Board

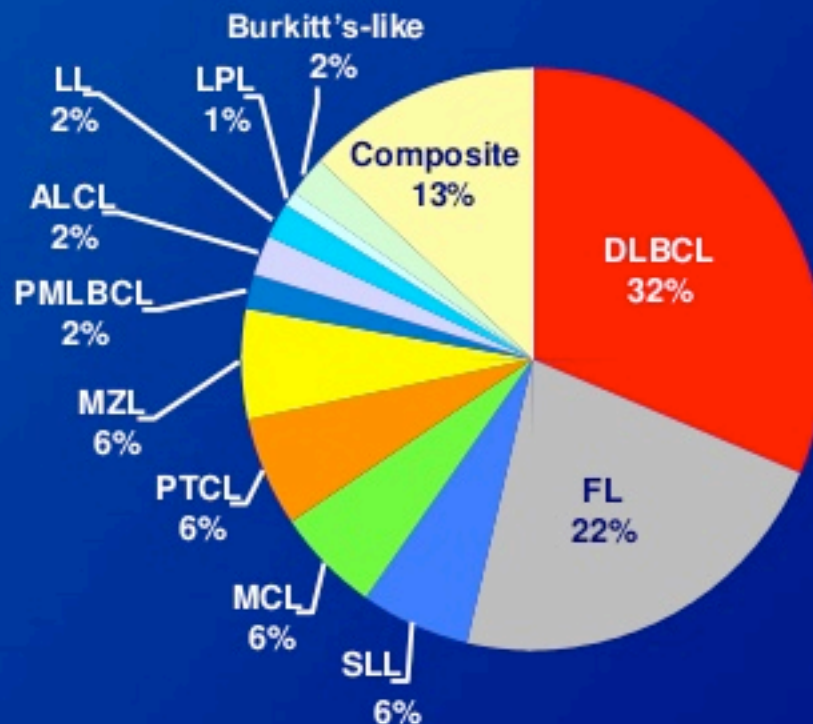
Friday, December 16, 2016

Background

- Rare: 1-4% of lymphomas, but may be underrecognized
- Two distinct lymphomas co-occurring in one patient
 - Metachronous
 - Synchronous
- Typically occur in the same organ
- Commonly comprise two subtypes of non-Hodgkin lymphoma, or the combination of a non-Hodgkin lymphoma and Hodgkin lymphoma
- No well-defined standard of care
- Tumors are often clonally related
 - In cases comprising the co-occurrence of non-Hodgkin with Hodgkin lymphoma, the malignant clones are thought to be derived from a common precursor, usually a germinal center B cell
- Lymph node or tissue biopsy remains mainstay of diagnosis

Relative Incidence of NHL Subtypes

>71,000 new cases in US in 2015



NHL = non-Hodgkin lymphoma; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma.
Armitage & Weisenburger, 1998; ACS, 2015.

IDENTIFICATION OF COMMON GERMINAL-CENTER B-CELL PRECURSORS IN
TWO PATIENTS WITH BOTH HODGKIN'S DISEASE AND NON-HODGKIN'S
LYMPHOMA

ANDREAS BRÄUNINGER, PH.D., MARTIN-LEO HANSMANN, M.D., JOHN G. STRICKLER, M.D., REINHARD DUMMER, M.D.,
GÜNTHER BURG, M.D., KLAUS RAJEWSKY, M.D., AND RALF KÜPPERS, PH.D.

Abstract

BACKGROUND: Hodgkin's disease and non-Hodgkin's B-cell lymphoma occasionally occur in the same patient. The identification of a common precursor of the two types of lymphoma would show definitively that Reed-Sternberg cells originate from B cells.

METHODS: We studied lymphomas from two patients, one with a composite lymphoma (classic Hodgkin's disease and a follicular lymphoma in the same lymph node) and the other with a T-cell-rich B-cell lymphoma that was followed by classic Hodgkin's disease. Single Reed-Sternberg cells and non-Hodgkin's lymphoma cells from frozen sections were micromanipulated. The rearranged immunoglobulin variable-region genes (V genes) of the heavy and light chains were amplified by the polymerase chain reaction from genomic DNA and sequenced.

RESULTS: In both patients, the Reed-Sternberg cells were related clonally to the non-Hodgkin's lymphoma B cells. The V genes carried somatic mutations (a hallmark of germinal-center B cells and their descendants). In both patients, some somatic mutations were shared by the Reed-Sternberg and non-Hodgkin's lymphoma cells, whereas other somatic mutations were found exclusively in one or the other cell type.

CONCLUSIONS: In two patients with classic Hodgkin's disease and non-Hodgkin's B-cell lymphoma, we identified a common B-cell precursor, probably a germinal-center B-cell, for both lymphomas. This finding suggests that the two types of lymphoma underwent both shared and distinct transforming events and provides proof of the B-cell derivation of Reed-Sternberg cells in classic Hodgkin's disease.

N Engl J Med. 1999 Apr 22;340(16):1239-47.

Figure 2

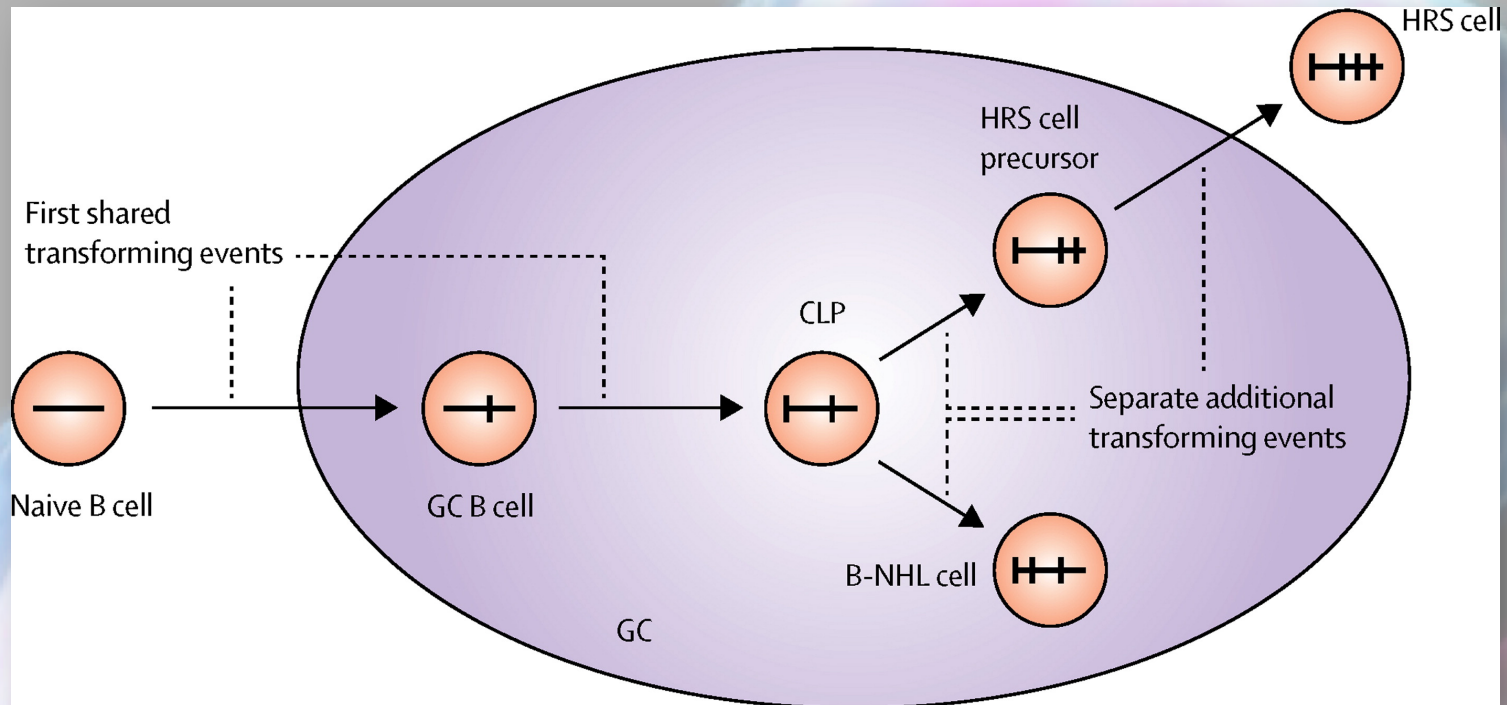


Figure 2: Scenario for generation of clonally related composite lymphomas of a Hodgkin's lymphoma and a B-non-Hodgkin lymphoma

Horizontal lines in the cells denote IgV genes, vertical lines V gene mutations. CLP=common lymphoma precursor. GC=germinal centre. NHL=non-Hodgkin lymphoma. HRS=Hodgkin and Reed-Sternberg.

Pathogenesis

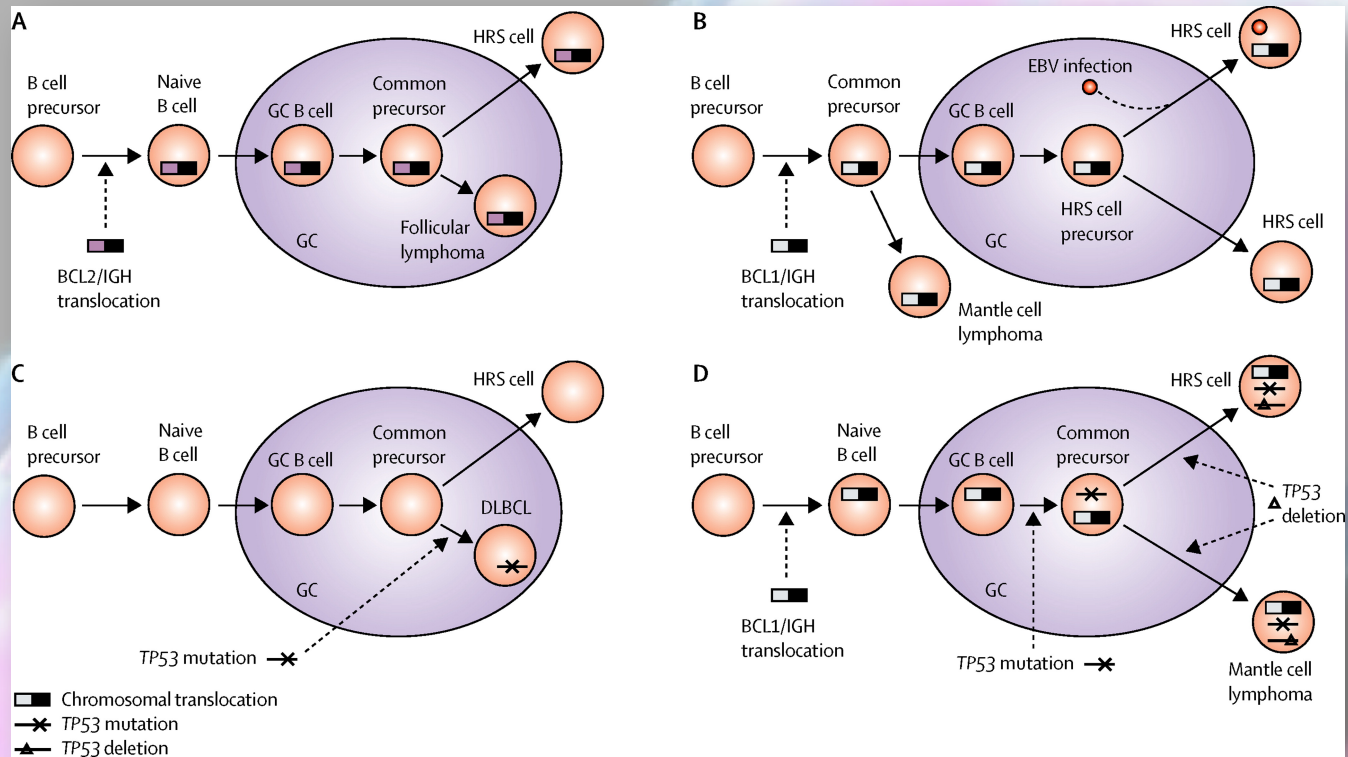


Figure 3: Transforming events during composite lymphoma pathogenesis

Several composite and sequential clonally related Hodgkin's lymphomas and B-non-Hodgkin lymphomas were studied for shared and distinct transforming events. (A) BCL2/IgH chromosomal translocations.^{22,54} (B) Chromosomal translocations with EBV infection.⁵⁴ (C) TP53 mutation.⁵⁴ (D) Chromosomal translocation with TP53 mutation and TP53 deletion on the other allele.²⁵ GC=germinal centre. HRS=Hodgkin Reed-Sternberg. DLBCL=diffuse large B-cell lymphoma. EBV=Epstein-Barr virus.

Pathology (1)

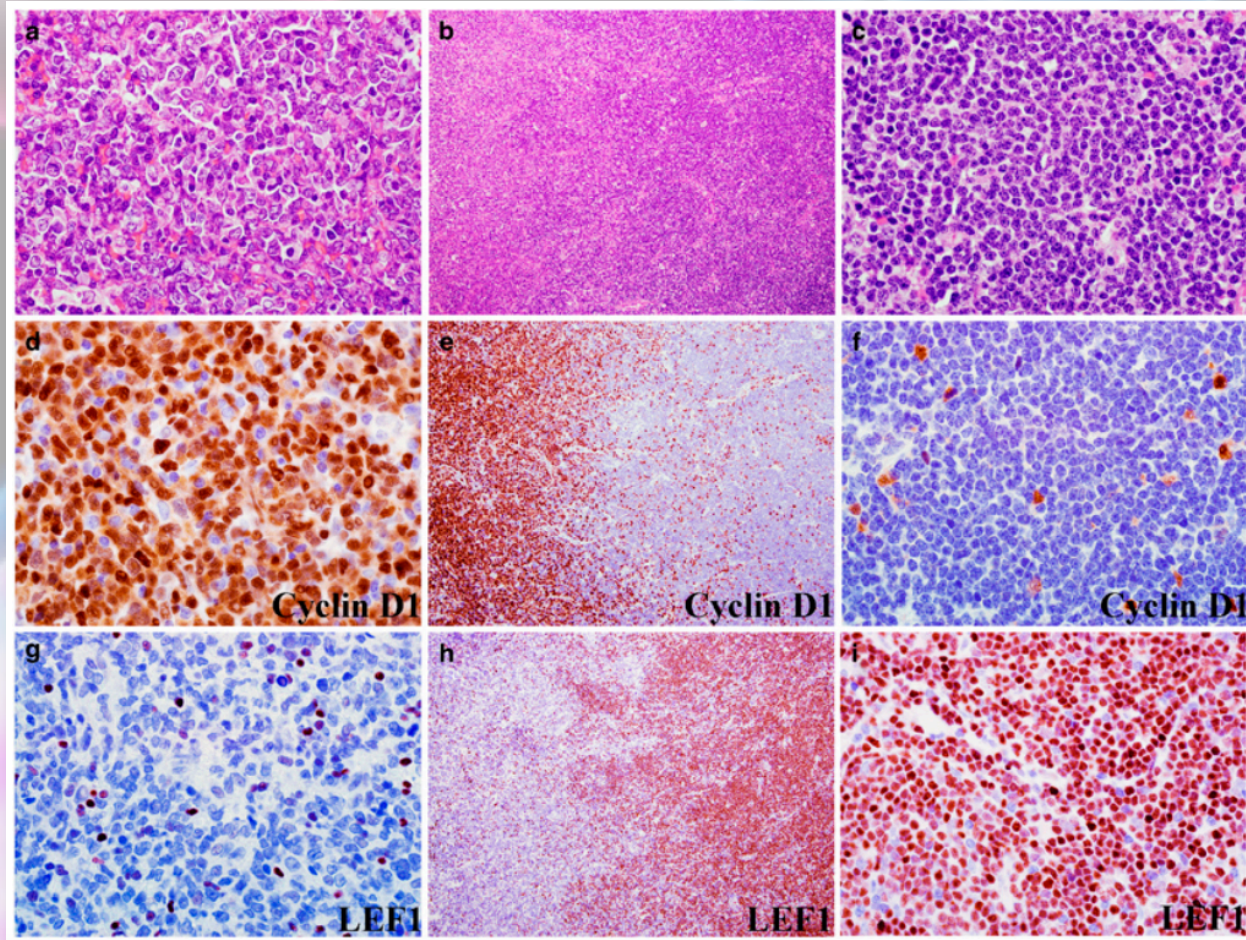


Figure 6: Composite lymphoma composed of small lymphocytic lymphoma and mantle cell lymphoma, pleomorphic type. Middle (b, e, h): low-power view of the lymph node biopsy (× 100); left (a, d, g): high-power view of the mantle cell lymphoma component (× 600); right (c, f, i): high-power view of the small lymphocytic lymphoma component (× 600). (a–c) Two distinct areas composed of large pleomorphic cells on the left and small lymphocytes on the right (H&E stain). (d–f) Immunostaining for cyclin D1 showed nuclear positivity in the large cell component on the left, consistent with mantle cell lymphoma. The small cell component on the right was negative. (g–i) Immunostaining for LEF1 demonstrated nuclear positivity in the small cell component (small lymphocytic lymphoma) on the right, but negative in the large cell component (mantle cell lymphoma) on the left.

Pathology (2)

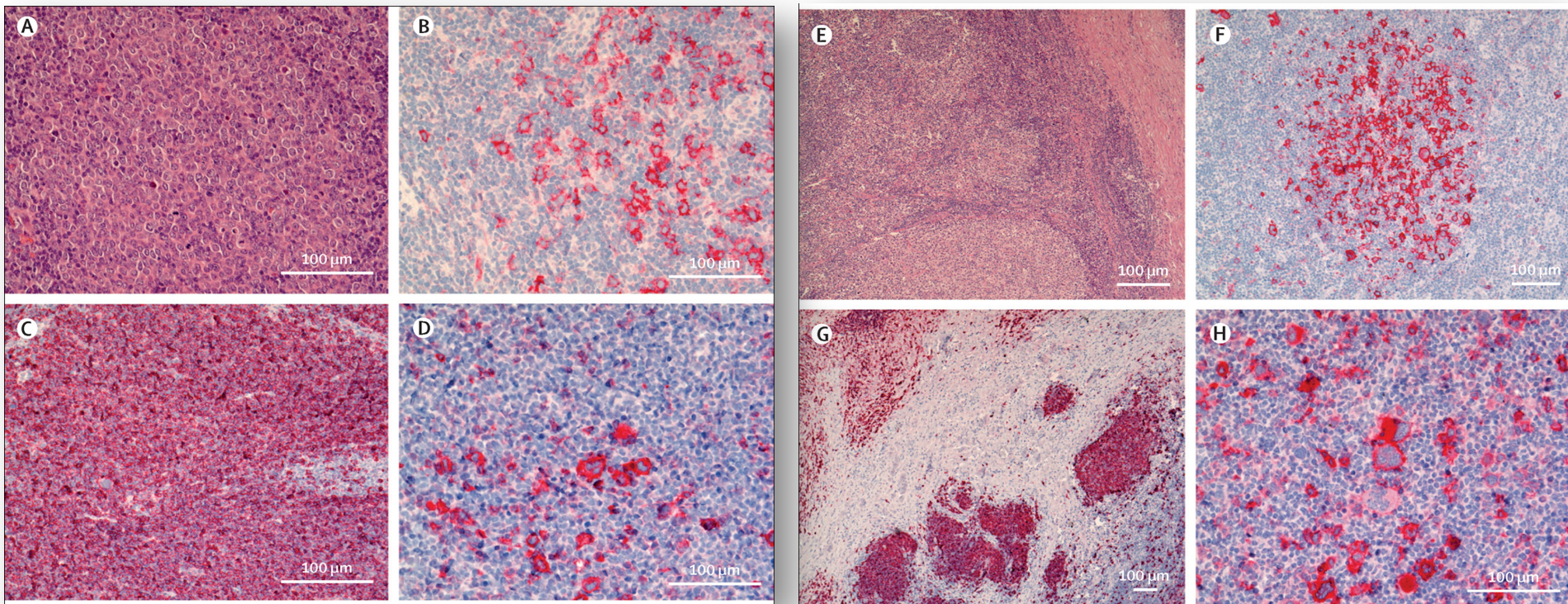


Figure 1: Histology and immunohistochemistry of composite lymphomas

DLBCL=diffuse large B-cell lymphoma. HRS=Hodgkin's and Reed-Sternberg. CD20 and CD30 were visualised by immunostaining. (A) and (B) Composite lymphoma of a DLBCL and a classic Hodgkin's lymphoma of nodular sclerosis type. 20× magnification. (A) Haematoxylin and eosin staining show DLBCL features. (B) CD30-positive HRS cells. (C) and (D) Composite lymphoma of a DLBCL and a classic Hodgkin's lymphoma. 20× magnification. (C) CD20-positive DLBCL cells. (D) CD30-positive HRS cells. (E) and (F) Composite lymphoma of a follicular lymphoma and a classical Hodgkin's lymphoma. (E) Follicular lymphoma, sclerotic band on the right side of the picture, haematoxylin and eosin staining, 4× magnification. (F) CD30-positive HRS cells. 10× magnification. (G) and (H) Composite lymphoma of a follicular lymphoma and a classical Hodgkin's lymphoma. (G) CD20-positive neoplastic follicles of the follicular lymphoma. In the middle of the picture, a pale CD20-negative area composed of a Hodgkin's lymphoma infiltrate is visible. 4× magnification. (H) CD30-positive HRS cells (from pale area of picture G). 20× magnification.

Cytogenetics – ALCL/DLBCL example

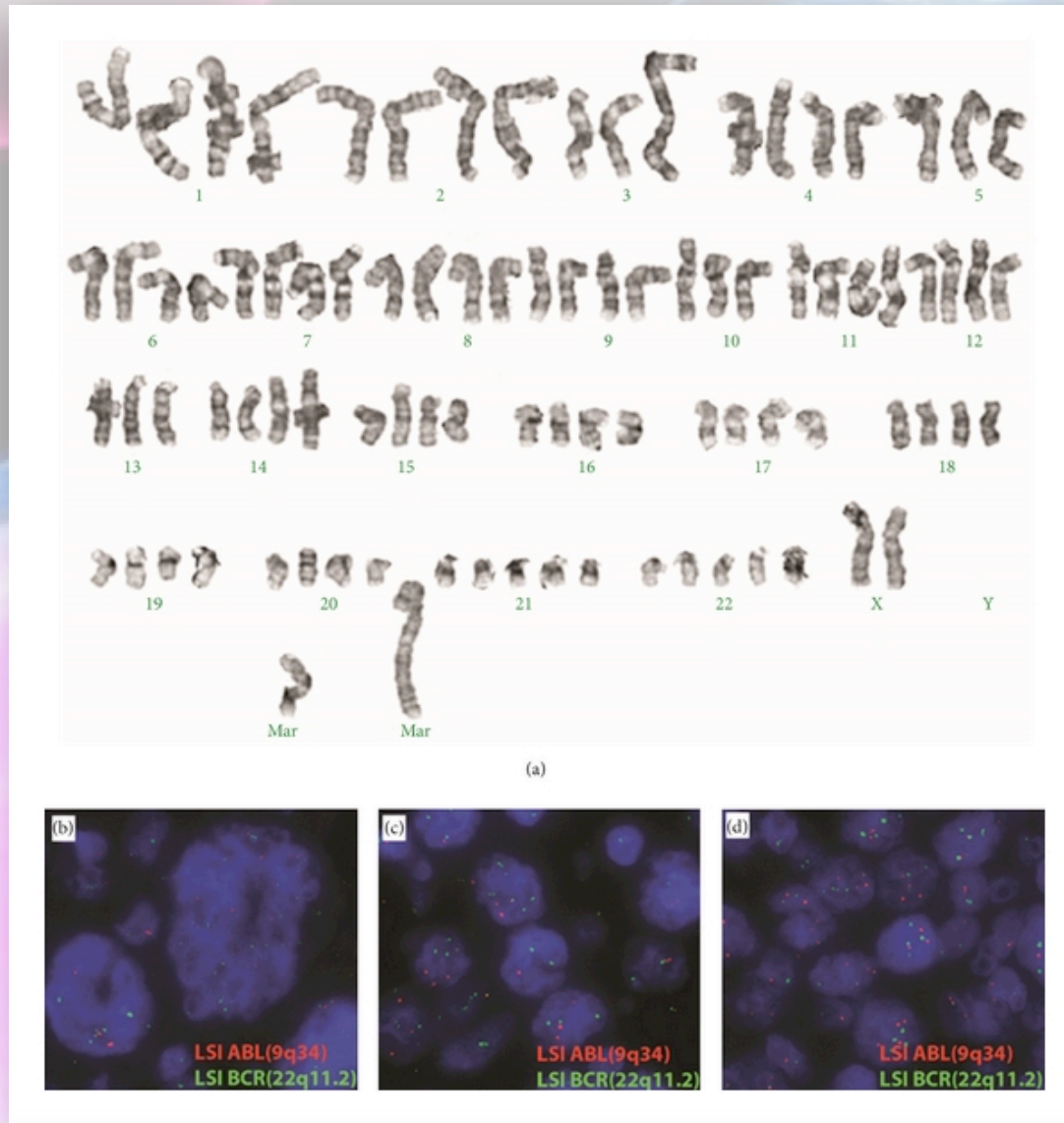


Figure 3: Conventional cytogenetics and FISH analysis of the lymphoma. (a) Representative karyotype showing complex numerical and structural abnormalities. (b) and (c) FISH analysis using LSI ABL (9q34, red) and LSI BCR (22q11.2, green) dual color probes shows approximately 3–8 signals for chromosome 9 (red) and chromosome 22 (green) in anaplastic large cell lymphoma-like area. (d) FISH analysis using the same probes shows approximately 4 signals for chromosome 9 (red) and chromosome 22 (green) in conventional diffuse large B-cell lymphoma area.

	Clonal relation	Description
Classic Hodgkin's lymphoma		
Follicular lymphoma ¹⁵	Yes	Shared and distinct V gene mutations
Follicular lymphoma ¹⁹	Yes	Shared and distinct V gene mutations
CLL ¹⁹	Yes	Shared and distinct V gene mutations; initial CLL diagnosis 5 years earlier
CLL ²⁰	No	..
CLL ²⁰	No	..
CLL ³⁰	No	..
DLBCL ¹⁶	Unknown	Two different V _H genes rearranged to the same D _H J _H joint; receptor revision in one clone, or separate development from a common pro-B cell
DLBCL ¹⁸	Yes	..
DLBCL ²³	Yes	Shared and distinct V gene mutations
CLL & anaplastic DLBCL ²⁷	Yes	Three lymphomas in one lymph node; identical V _H mutation pattern
MCL ²⁵	Yes	Only shared mutations
MCL ²⁶	Yes	HRS cells with IgV gene mutations, mantle cell lymphoma unmutated
MCL ²⁹	No	..
MCL ²⁹	No	..
T-cell NHL ²⁸	No	..
Low-grade B-cell NHL ³⁰	Yes	..
Low-grade B-cell NHL ³⁰	Yes	..
High-grade B-cell NHL ³⁰	No	..
Cutaneous T cell LPD ³¹	Yes	Hodgkin's lymphoma in lymph node; T-cell origin of both lymphomas
Nodular lymphocyte predominant Hodgkin's lymphoma		
DLBCL ³²	Yes	..
TCRBCL ³³	Yes	..
Classic Hodgkin's lymphoma ³⁴	Yes	Clonality based on two identically sized VκJκ joints, not on sequencing
Classic Hodgkin's lymphoma ³⁵	Yes	Shared mutations (short sequence)

MCL=mantle cell lymphoma. CLL=chronic lymphocytic leukaemia. DLBCL=diffuse large B-cell lymphoma. LPD=lymphoproliferative disorder. NHL=non-Hodgkin lymphoma. TCRBCL=T-cell-rich B-cell lymphoma. HRS=Hodgkin and Reed-Sternberg cells. LP=lymphocyte predominant cells. *Only cases in which at least the HRS or LP cells were microdissected for molecular analysis are considered.

Table 1: Composite Hodgkin's and non-Hodgkin lymphomas for which the clonal relations was clarified*

	Clonal relation	Description
Classic Hodgkin's lymphoma		
TCRBCL ¹⁵	Yes	HL developed 3 years after TCRBCL; shared and distinct V gene mutations
Follicular lymphoma ²¹	Yes	Follicular lymphoma developed two years after HL; shared and distinct V _H gene mutations
Follicular lymphoma ²²	Yes	HL diagnosed 4 years after follicular lymphoma
SMZL ²⁴	Yes	HL developed 15 years after SMZL; both lymphomas had unmutated V _H region genes
DLBCL ⁴⁴	No	DLBCL diagnosed 12 years after initial HL diagnosis
Small non-cleaved cell B-cell NHL ⁴⁰	No	B-cell NHL developed 6 years after HL
MALT lymphoma and anaplastic DLBCL ⁴¹	No	MALT lymphoma 4 years before and DLBCL 2 years after HL; NHL clonally related to each other
marginal zone & T-cell NHL ⁴³	No	T-cell NHL first diagnosed 30 years before the other lymphomas, which occurred concurrently
PMBCL ⁴⁷	Yes	HL developed after PMBCL
PMBCL ⁴⁷	Yes	PMBCL developed after HL
PMBCL ⁴⁸	Yes	PMBCL developed after HL; confirmation of clonal relationship mainly based on shared chromosomal lesions
CLL ¹⁷	No	HL developed 4 years after CLL
CLL ¹⁷	No	HL developed 5 years after CLL
CLL ³⁹	Yes	HL developed 4 years after CLL
CLL ³⁹	Yes	HL developed 8 years after CLL
CLL ³⁹	No	HL developed 10 years after CLL
CLL ⁴⁵	No	HL diagnosed 10 years after CLL
Lymphomatoid papulosis and cutaneous T-cell lymphoma ⁴⁶	Yes [†]	HL developed 4 years after lymphomatoid papulosis and was followed 10 years later by a cutaneous T-cell lymphoma
Nodular lymphocyte predominant Hodgkin's lymphoma		
DLBCL ³²	Yes	DLBCL developed 34 months after NLPHL
TCRBCL ⁴²	Yes	TCRBCL developed 4 years after NLPHL; shared and distinct V gene mutations

CLL=chronic lymphocytic leukaemia. DLBCL=diffuse large B-cell lymphoma. HL=Hodgkin's lymphoma. PMBCL=primary mediastinal B-cell lymphoma. SMZL=splenic marginal zone lymphoma. TCRBCL=T-cell-rich B-cell lymphoma. NHL=non-Hodgkin lymphoma. HRS=Hodgkin and Reed-Sternberg cells. LP=lymphocyte predominant cells. *Only cases in which at least the HRS or LP cells were microdissected for molecular analysis are considered. †Although HRS cells were not microdissected for molecular analysis, this case is included, because at time of diagnosis of Hodgkin's lymphoma no T-cell malignancy as a potential source for contamination in the PCR analysis was evident in the patient.

Table 2: Clonal relation between Hodgkin's and non-Hodgkin lymphomas developing consecutively in a patient*

	Type and presence of transforming event	Description
Classical HL; DLBCL ¹⁸	EBV positive; EBV negative	..
Classical HL; follicular lymphoma ²²	t(14;18), BCL2/IgH; t(14;18), BCL2/IgH	Identical translocation
Classical HL; MCL ²⁵	t(11;14), BCL1/IgH, TP53 deletion and mutation; t(11;14), BCL1/IgH, TP53 deletion and mutation	Identical translocation, identical TP53 point mutation, but presumably distinct deletion of other TP53 allele
Classical HL; MCL ^{26,54}	t(11;14), BCL1/IgH, subclone EBV positive; t(11;14), BCL1/IgH, EBV negative	Identical translocation, HRS cell subclone with distinct V _H mutations EBV positive
Classical HL; NLP HL ³⁵	EBV positive; EBV negative	..
Classical HL; CLL ³⁹	EBV positive; EBV negative	HL developed after CLL
Classical HL; CLL ³⁹	EBV positive; EBV negative	HL developed after CLL
Classical HL; follicular lymphoma ⁵⁴	t(14;18), BCL2/IgH; t(14;18), BCL2/IgH	Identical translocation
Classical HL; follicular lymphoma ⁵⁴	t(14;18), BCL2/IgH; t(14;18), BCL2/IgH	Identical translocation
Classical HL; DLBCL ⁵⁴	TP53 mutations negative; TP53 mutations positive	..

HRS=Hodgkin and Reed-Sternberg cells. EBV=Epstein-Barr virus. Ig=immunoglobulin. HL=Hodgkin's lymphoma. DLBCL=diffuse large B-cell lymphoma. MCL=mantle cell lymphoma. CLL=chronic lymphocytic leukaemia. NLP HL=nodular lymphocyte predominant Hodgkin's lymphoma.

Table 3: Shared and distinct genetic lesions and viral infections in clonally related composite or consecutive Hodgkin's lymphoma and B-cell non-Hodgkin lymphoma

Treatment - Principles

- Overall therapeutic strategy needs to consider both disease components
- Current first-line chemotherapy protocols are based on alkylating agents
- Indolent lymphomas: 6 cycles of bendamustine and rituximab induce remissions in 90% of patients
 - Remission can be prolonged by using anti-CD20 maintenance therapy
- Aggressive lymphomas: alkylating agents combined with anthracyclines, glucocorticoids, and other agents
- CD20⁺ B-cell lymphomas: alkylating agents are combined with antibodies directed against CD20
- DLBCL: 6 to 8 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) is standard of care
- CD20⁻ lymphomas: treatment is tailored to size of tumor mass
 - ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) or BEACOPP for more advanced stages (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)

Maintenance rituximab following induction R-CHOP chemotherapy in patients with composite or discordant, indolent and aggressive, B-cell non-Hodgkin lymphomas

*Roopesh Kansara,¹ Joseph M. Connors,¹ Kerry J. Savage,¹
Alina S. Gerrie,^{1,2} David W. Scott,¹ Graham W. Slack,³
Randy D. Gascoyne,³ Laurie H. Sehn,¹ and Diego Villa¹*

¹Centre for Lymphoid Cancer and Department of Medical Oncology, British Columbia Cancer Agency; ²Leukemia/Bone Marrow Transplant Program of British Columbia, British Columbia Cancer Agency; and ³Centre for Lymphoid Cancer and Department of Pathology and Laboratory Medicine, British Columbia Cancer Agency, Vancouver, BC, Canada

*Correspondence: dvilla@bccancer.bc.ca
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Key words: composite lymphoma, discordant lymphoma, transformed lymphoma, maintenance rituximab, R-CHOP

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Treatment – Patient Characteristics

Table 1. Baseline patients' characteristics according to diagnosis: composite (COM) versus discordant (DIS) lymphoma.

Characteristics	Composite N=58	Discordant N=40	P
Age			
≤ 60 years	29 (50%)	11 (28%)	0.026
> 60 years	29 (50%)	29 (72%)	
Sex			
Male	30 (52%)	25 (63%)	0.291
Female	28 (42%)	15 (38%)	
Performance status			
0 – 1	47 (81%)	22 (55%)	0.006
≥ 2	11 (19%)	18 (45%)	
Lactate dehydrogenase			
Normal	35 (64%)	14 (35%)	0.006
Elevated	20 (36%)	26 (65%)	
Ann Arbor Stage			
III	13 (22%)	0	<0.001
IV	45 (78%)	40 (100%)	
Number of extranodal sites			
< 2	48 (83%)	18 (45%)	<0.001
≥ 2	10 (17%)	22 (55%)	
IPI			
Low	17 (29%)	3 (8%)	<0.001
Low-intermediate	18 (33%)	7 (18%)	
High-intermediate	17 (31%)	11 (27%)	
High	3 (6%)	19 (47%)	
Largest tumor mass			
< 10 cm	40 (49%)	29 (73%)	0.706
≥ 10 cm	18 (31%)	11 (27%)	
Type of indolent NHL			
Follicular	53 (91%)	15 (37%)	<0.001
Low grade, NOS	0	25 (63%)	
Marginal zone	4 (7%)	0	
Lymphoplasmacytic	1 (2%)	0	
Bone marrow involvement			
Indolent NHL	13 (22%)	34 (85%)	<0.001
DLBCL	5 (9%)	2 (5%)	
Negative	40 (69%)	4 (10%)	
Response to R-CHOP			
Complete	47 (81%)	30 (75%)	0.474
Partial	11 (19%)	10 (25%)	
Maintenance rituximab			
No	18 (31%)	25 (63%)	0.002
Yes	40 (69%)	15 (37%)	

IPI: International Prognostic Index; NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified.

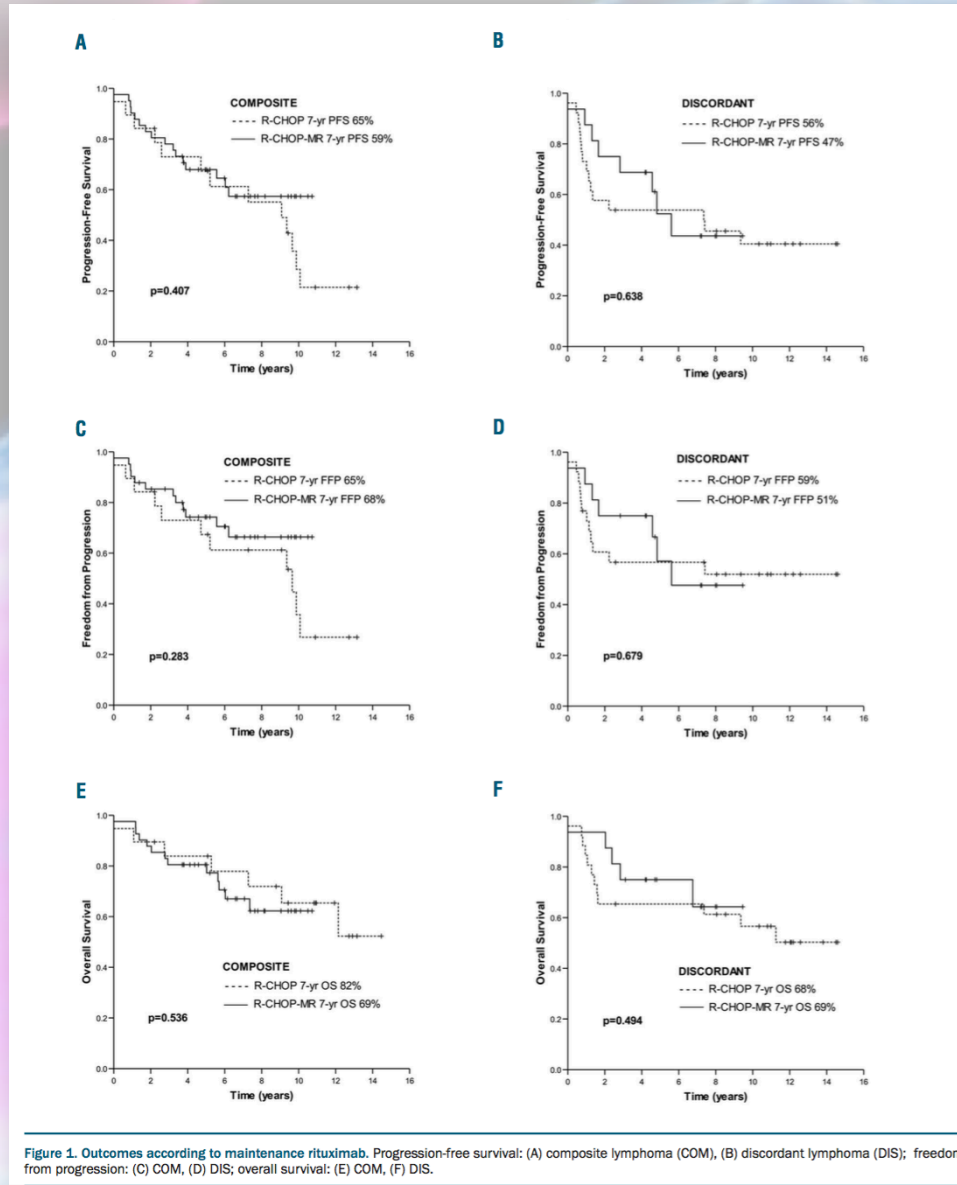
Treatment - Patient Characteristics (2)

Table 2. Baseline patients' characteristics according to maintenance rituximab.

Characteristics	Pre-policy R-CHOP only N=43	Post-policy R-CHOP + MR N=55	P
Age			
≤ 60 years	19 (44%)	21 (38%)	0.548
> 60 years	24 (56%)	34 (62%)	
Sex			
Male	27 (63%)	28 (51%)	0.240
Female	16 (37%)	27 (49%)	
Performance status			
0 – 1	25 (58%)	44 (80%)	0.019
≥ 2	18 (42%)	11 (20%)	
Lactate dehydrogenase			
Normal	21/42 (50%)	28/53 (53%)	0.784
Elevated	21/42 (50%)	25/53 (47%)	
Ann Arbor Stage			
I/II	5 (12%)	8 (15%)	0.673
III/IV	38 (88%)	47 (85%)	
Extranodal sites			
< 2	25 (61%)	38 (70%)	0.395
≥ 2	16 (39%)	16 (30%)	
IPI			
Low	9/42 (21%)	13/53 (24%)	0.401
Low-intermediate	11/42 (26%)	15/53 (27%)	
High-intermediate	10/42 (23%)	18/53 (33%)	
High	13/42 (30%)	9/53 (16%)	
Largest tumor mass			
< 10 cm	31 (72%)	38 (69%)	0.434
≥ 10 cm	12 (28%)	17 (31%)	
Diagnosis			
Composite NHL	18 (42%)	40 (73%)	0.002
Discordant NHL	25 (58%)	15 (27%)	
Type of indolent NHL			
Follicular	23 (53%)	44 (80%)	0.021
Low grade, NOS	17 (40%)	8 (14%)	
Marginal zone	3 (7%)	2 (4%)	
Lymphoplasmacytic	0	1 (2%)	
Bone marrow involvement			
Indolent NHL	27 (56%)	20 (36%)	0.027
DLBCL	3 (7%)	4 (7%)	
Negative	13 (30%)	31 (56%)	
Response to R-CHOP			
Complete	36 (84%)	41 (75%)	0.272
Partial	7 (16%)	14 (25%)	

IPI: International Prognostic Index; NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; NOS: not otherwise specified.

Treatment Outcome – PFS and OS



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