Title:
Clonal Relationship of Classical Hodgkin Lymphoma and its Recurrences

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Classical Hodgkin lymphoma, clonal relationship, laser capture microdissection, immunoglobulin heavy chain rearrangement, Epstein Barr virus-association

Statement of Translational Relevance
Our finding that not all recurrent Hodgkin lymphomas (HL) are true “relapses” of the original malignant clone may be of clinical significance in that it raises questions about the current aggressive clinical therapies in such instances, suggesting that clonally unrelated relapsed HL might still qualify for less intensive therapeutic approaches. Moreover, our findings provide further evidence of the interplay between individual predisposition and of the possible presence of clonotypic lymphoma progenitor cells in the pathogenesis of HL.
Abstract

Purpose: We investigated whether the first and all subsequent manifestations of Hodgkin lymphoma (HL) in a patient are clonally related.

Experimental Design: We identified a collective of 20 patients with sometimes multiple HL recurrences. Relapses were classified as early, i.e. within twelve months (eight events in seven patients) or as late, i.e. later than one year after the previous neoplasm (24 events in 17 patients). Hodgkin and Reed-Sternberg cells were microdissected after CD30 staining using laser-capture technique. *Immunoglobulin heavy chain* (*IgH*) gene fragment lengths were analyzed after DNA pre-amplification, applying consensus FR3 and J primers by ABI 310 Genetic Analyzer. Sequencing of the amplified *IgH* products was performed by ABI 3130 and 3730XL Genetic Analyzer. Epstein-Barr virus (EBV)-association was assessed by EBER and LMP1.

Results: Three cases with early relapses after a first HL diagnosis were clonally related to the initial tumor, while three of four patients with early relapses after a first or second relapse were not, which was accompanied by change of EBV-association in one case. Six patients presenting with late relapses were clonally unrelated, which was accompanied by change of phenotype in two cases and change of EBV-association in one case. Two samples from recurrent tumors of a same patient could be successfully sequenced. These two late relapses were clonally unrelated by *IgH* fragment length- and sequencing analysis.

Conclusions: Recurrent HL, especially those accompanied by an EBV-association switch or after a relapse, can represent an unrelated novel neoplasm. Our finding might play a role in clinical decision making.

Introduction

Classical Hodgkin lymphoma (HL) is a highly curable malignancy when treated with multi-modal therapy (1). However, up to 30% of patients fail to respond or suffer a relapse after initial therapy (2-4). Intensive chemotherapy with or without autologous stem cell support is now the treatment of choice for patients with relapsed, chemosensitive HL (5,6).

Hodgkin and Reed-Sternberg cells represent the tumor cell population of HL. Both B-cell origin and monoclonality of Hodgkin and Reed-Sternberg cells have been established (reviewed in: 7). It has also been shown that in composite lymphomas,
consisting of a HL and a so-called “non-Hodgkin lymphoma” (NHL), a clonal relationship between both components can exist (8-11), but studies on the clonal relationship of recurrent HL have so far been limited to case reports (12). Our aim was to specifically analyze the clonal relationship of recurrent HL by several molecular techniques in addition to morphology, phenotype and Epstein-Barr virus (EBV)-association. The study reported herein assessed the clonal relationships of the largest number of recurrent HL analyzed to date.

Methods

Patients

Patients with recurrent HL were identified from the archives of the Institutes of Pathology in Basel, Bern, and Liestal (all in Switzerland). Tissue samples of the identified patients were included in our analysis if adequately preserved for immunohistochemical and molecular analyses. Clinical and follow-up data were obtained by reviewing the charts. Retrieval of tissue and clinical data were performed according to data safety laws.

Histopathology, Immunohistochemistry and in situ Hybridization

All cases were reclassified according to the most recent WHO criteria (13). Four-micrometer sections were cut from routinely-processed, formalin-fixed and paraffin-embedded specimens placed on adhesive-coated slides. The slides were immunohistochemically stained using an automated immunostainer (BenchMark XT, Ventana, USA). The following primary antibodies were utilized: CD30 (clone Ber-H2; catalogue no. 790-2926, Ventana, dilution as supplied), and LMP1 (clone CS1-4, catalogue no. CMC426, Cell Marque, USA, dilution 1:25). No counterstain was used in case of the CD30 staining.

In situ hybridization for EBV early RNA (EBER) was performed on deparaffinized and dehydrated sections. Chromogen-labeled oligonucleotides complementary to portions of the EBV-encoded early RNA transcripts (Inform probe, ref. 800-2842, Ventana, USA), were used according to the manufacturer’s protocol. Positivity was defined as clear labeling of all Hodgkin and Reed-Sternberg cells per slide.

Microdissection and molecular analysis
Laser-capture microdissection similar to that described previously was performed (8). Briefly, uncovered and un-counterstained tissue slides stained for CD30 were utilized. CD30-positive cells were identified, separated by laser beam from the surrounding tissue and catapulted into the lid of an Eppendorf cup with aid of the PalmRoboSoftware 3.0 on a PALM MicroBeam-System (Zeiss, Germany).

DNA from the microdissected Hodgkin and Reed–Sternberg cells was extracted using a Genovison extraction kit (Qiagen, Germany), as described (8). Pre-amplification was performed using the REPLI-g FFPE Kit (Qiagen) according to the manufacturer’s instructions.

Polymerase chain reaction (PCR) analysis of immunoglobulin heavy chain (IgH) gene rearrangements was performed utilizing consensus FR3 and J primers, as published previously (14). To verify results, a second PCR with a different set of primers was carried out. This second experiment utilized primers designed to give four base pairs (bp) shorter PCR products than the products from the first PCR (Primer sequence: for IgH FR3: FR3C ACACGCGYGTGTATTACTGT labeled with 6-FAM, and for IgH J: JOIN A - CCTGAGGAGACGGTGACC, JOIN B - CCTGAAGAGACGGTGACCA, JOIN C - CCTGAGGAGACGGTGACCA). Examination of PCR products was carried out with the high resolution fragment length analysis (ABI 310 Genetic Analyzer, Applied Biosystems, USA). Clonality was assumed by the demonstration of a peak in the initial PCR run and a peak belonging to a PCR product, which was four bp shorter in the verification PCR than in the initial PCR. A shift of the PCR products of more than one bp between the cases was considered to indicate a clonally unrelated event.

Sequencing of the amplified IgH gene FR3 region products was performed, both in our institution and by a commercial company (Microsynth, Switzerland, www.microsynth.ch) in 45 samples of all patients, where DNA was available after IgH fragment length analysis. Sanger sequencing was performed with the laser-induced fluorescence detection system ABI 3130 and 3730XL Genetic Analyzer and the corresponding software (Applied Biosystems).
Results

Patients

Altogether, a total number of 20 patients with recurrent HL were collected from the Institutes of Pathology in Basel (n=12), Bern (n=3), and Liestal (n=5). In five patients it was not possible to evaluate the initial HL, but since it was possible to assess the following recurrences, these cases were not excluded (no. 11, 15-17, 20). The patients with evaluable tumors were comprised of twelve males (average age at diagnosis 32; range: 5-67) and eight females (average age at diagnosis: 44; range: 20-86).

An overview of all cases with the number and chronology of recurrences is presented in Figure 1 and Table 1. Twelve patients had one recurrence (no. 1, 2, 4-10, 12, 13 and 18), five patients experienced two recurrences (no. 3, 11, 16, 19 and 20), two patients had three recurrences (no. 14 and 17), and one patient had four recurrences (no. 15). There were early relapses in seven patients [no. 1-3, 11, 14, 15 and 20; including two subsequent early relapses (no. 3)], i.e. three early relapses after first HL diagnosis (no. 1-3), five early relapses after a relapse (no. 3, 11, 14, 15 and 20), and late recurrences in 17 patients (no. 4-20). In one case (no. 5), the recurrent HL was preceded by a follicular lymphoma, grade 2, which had occurred eight years before the first diagnosis of HL.

Two further cases were also analyzed: One patient (no. 21; male; age at diagnosis: 45) had originally presented with a HL (mixed cellularity subtype), followed by a diffuse large B-cell lymphoma (DLBCL) two years later. The second patient (no. 22; female, age at diagnosis: 69) had a DLBCL initially that recurred as a HL (mixed cellularity subtype) six years later.

All patients were treated with intention to cure. At the point of last clinical contact, out of all 22 patients, 17 are still alive, while five have died of their disease. Clinical details, including the type of therapy administered, are presented in Table 1.

Histopathology, Immunohistochemistry and in situ Hybridization

Sixteen HL presented initially as nodular sclerosis- (no. 1-6, 8, 9, 11-16, 18 and 19), and four cases as mixed cellularity subtype (no. 7, 10, 20 and 21). It was not possible to get information on the initial subtype in one case (no. 17). A change of subtype was demonstrated in six cases (no. 5, 9, 14, 16, 18 and 20).
EBV-association was evaluable in all cases: In 15 patients, all initial disease and recurrence(s) were EBER and LMP1-negative (no. 1-6, 8, 10, 12, 15-20). A switch from EBER/LMP1 negativity to positivity was observed in one patient (no. 14). Interestingly, one patient (no. 11) who presented with simultaneous recurrences at two different anatomic regions had both an EBER/LMP1-positive and an EBER/LMP1-negative tumor at each site. The patient with recurrent HL preceded by follicular lymphoma (no. 5) and the two patients with composite DLBCL and HL (no. 21 and 22) were EBER/LMP1-negative in all tumors.

**Microdissection and Molecular Analysis**

Analysis of *IgH* fragment length was successful in all patients (Figure 1). On average, it was possible to microdissect 350 Hodgkin and Reed–Sternberg cells per sample. In two cases (first relapse of no. 14 and third relapse of no. 15, both with irresolute PCR results), up to approximately 500 cells per case were microdissected. In three samples (first and second relapse of no. 3 and fourth relapse of no. 15, the latter with irresolute PCR results), due to the small size of the diagnostic sample, the whole tissue section was used without microdissection.

By *IgH* fragment length analysis all three early relapses after first HL diagnosis were clonally related to their initial tumor (no. 1-3), while three of four early relapses after a first or second relapse were not (no. 11, 14 and 20); one of the latter patients had two simultaneous clonally unrelated early second relapses (after first recurrence) at different anatomical sites and with divergent EBV-association (no. 11). Six of 20 analyzable late relapses were clonally unrelated, which was accompanied by a switch of phenotype in two cases (no. 6 and 14) and a change of EBV-association in one case (patient no. 14). All other late recurrences were clonally related to the initial HL (Figure 2). In the case of recurrent HL preceded by a follicular lymphoma, both HL were clonally related to each other despite a switch of phenotype; however, the preceding follicular lymphoma was not related to the HL. The two composite cases, initially presenting as HL and relapsing as DLBCL or vice versa, showed clonal relationships between both entities.

Sequencing of the amplified *IgH* gene FR3 region products was performed in 45 samples of patients no. 1 to 20, but yielded interpretable results confirming *IgH*-derived gene sequences in ten samples from nine patients (no. 1, 4, 5, 8, 11, 14, 15, 18 and 19) due to too low DNA amounts (picogram range instead of required...
nanogram range). However, two samples from recurrent tumors of a same patient (no. 15) could be successfully sequenced. These two late relapses were clonally unrelated, both by IgH fragment length- and sequencing analysis (Figure 3).

**Summary and Conclusions**

To our knowledge, this is the largest study to date assessing the clonal relationship of recurrent HL. We provide strong evidence - supported in one case also by gene sequencing - that not all cases of recurrent HL are true clonal “relapses” of the original malignant clone. There are three findings that support the existence of a second, non-related neoplasia: 1.) change of histological subtype, 2.) altered EBV-association, and, most important, 3.) clonal diversity as demonstrated by different IgH fragment lengths in eight cases as well as different IgH gene sequences in one case. Change of morphological subtype has been previously noted in recurrent HL, but has not been taken as a sign of lacking relationship because treatment might change the appearance of the lymphoma (15). This hypothesis is supported by our finding of molecular kinship in morphologically different tumor recurrences (e.g. no. 5, 9 and 18).

Assessment of EBV-association has been used to assess clonal relationship of recurrent HL, and these authors found a high correlation between expression of LMP1 in primary and recurrent HL (15). We observed a change of EBV-association (EBER and LMP1 expression) in two patients (no. 11 and 14), which is in accordance to the literature (16). Although at least in our series both patients with and EBV-association switch had clonally unrelated HL relapses, a positive or negative correlation of EBV-association will not prove beyond doubt the kinship of the tumors, particularly considering the possibility of EBV “hit and run” mechanisms in HL (11,17).

Analyzing IgH rearrangements seems to be the most accurate way to determine the clonal relationship of a recurrent lymphoma. In HL however, the scarcity of Hodgkin and Reed-Sternberg cells is a major drawback. A previous study focusing on HL with numerous Hodgkin and Reed-Sternberg cells showed that six of seven cases contained clonally related rearranged IgH- or light-chain genes (16). However, the authors analyzed whole samples in all cases rather than, as we did with the exception of three samples, laser-microdissected Hodgkin and Reed-Sternberg cells. In addition to these three samples, of which one was not analyzable and two showed clonal relationship to the microdissected initial diagnosis, and thus did not blur our
results, one potential limitation of our study should be addressed; namely, the low amount and poor quality of the DNA (due to scarcity of Hodgkin and Reed-Sternberg cells, small core needle biopsies obtained in relapsing HL, application of laser beam for microdissection and the archival nature of the samples), which though permitting result interpretation with the sensitive methodology of IgH fragment length analysis, allowed successful sequencing (more specific methodology) only in ten samples of nine patients. Importantly and supporting the validity of our results, in all these ten instances sequencing confirmed IgH derived genetic material. Yet, in one matching patient with two recurrences (no. 15), whose probes were analyzable by both methodologies, both results were concordant, i.e. clonally unrelated HL relapses (Figure 3), suggesting reliability of the platforms used. Furthermore, while somatic mutations are almost always detectable in the tumor cells of nodular lymphocyte predominant HL, this seems not be a genuine feature of Hodgkin and Reed-Sternberg cells of classical HL (18). Thus, ongoing mutations can probably not explain the observed IgH length changes in our bona fide clonally unrelated cases, supporting our assumption of existing cases of clonally unrelated relapsing HL. Nevertheless, our findings of clonally unrelated relapses raise two important issues. First, this might be of clinical importance since relapsing HL are treated aggressively without regard to the possibility of dealing with a second, newly developed, tumor. Thus, our findings may merit consideration in future clinical study to determine if a less intensive treatment might be justifiable in “recurrent” non-clonally related HL. Second, the underlying mechanism of HL relapses needs to be defined. It is possible to hypothesize the existence of Hodgkin and Reed-Sternberg cells, which are not altogether eliminated by therapy. Hodgkin and Reed-Sternberg cells are known for their defective cell cycle and apoptosis regulation, which enables them to escape therapy (reviewed in: 7), a theory which is supported by our finding of clonally-related recurrences. Another hypothesis focuses on the existence of tumor stem cells in HL. Such cells represent a small, but significant, population in tumors that possess both tumor-initiation and self-renewal capacity; tumor stem cells have been identified in several human malignancies (19) and are suspected in HL (11). Recently, the existence of a clonotypic lymphoid cell population that morphologically does not resemble Hodgkin and Reed-Sternberg cells has been proven (20); these cells may give rise to a clonally-related recurrence of HL as well. In support of the possibility of the existence of tumor stem- or precursor cells in HL, we and others have shown that
a clonal relationship can exist even between a HL and a metachronous NHL in the same individual (reviewed in: 21). Both genetic and environmental factors may predispose an individual to develop a HL; the relative risk of HL being highest (approximately 100-fold) in monozygous twins (22-25). Such predisposing factors might also increase the risk for a second HL in patients with “recurrent” disease, as observed also in our cohort, especially with second and third recurrences after a relapse. It is tempting to hypothesize that such individuals may be prone to develop a HL, and that environmental factors, including the adverse effects of previous intensive treatment, might enhance this predisposition.

In summary, this is the largest study we are aware of to date, evaluating at the genetical level the clonal relationship of recurrent HL. By analyzing \( \text{IgH} \) fragment lengths we provide strong evidence in eight patients that not all “relapses” are clonally related to the primary neoplasm. In one patient we further support this theory by sequencing of the \( \text{IgH} \) gene. These findings are interesting both in regard to different theories on relapsing HL and might have a practical implication on treatment strategies needing further evaluation.

**Disclosure of Potential Conflicts of Interest**

The authors do not have any potential conflicts of interest.

Parts of the study have been presented at the annual meeting of the German Society of Pathology in 2010 and published as a short communication in *Der Pathologe 2010;31 Suppl 2:132-3.*
Table legends

Table 1: Patient characteristics

Abbreviations:
ABVD: Adriamycin, Bleomycin, Vinblastine, Dacarbazine
ALLO-SCT: Allogeneic stem cell transplantation
AUTO-SCT: Autologous stem cell transplantation
BEACOPP: Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone
BEACOPPesc: BEACOPP escalated
BEAM: Carmustine, Etoposide, Cytarabine, Melphalan
CHOP: Cyclophosphamide, Adriamycin, Vincristine, Prednisone
COPP: Cyclophosphamide, Vincristine, Procarbazine, Prednisone
DHAP: Cytarabine, Cisplatin, Dexamethasone
F: Female
ICE: Ifosfamide, Carboplatin, Etoposide
IMVP16: Ifosfamide, Methotrexate, Etoposide
M: Male
MOPP: Mechlorethamine, Vincristine, Procarbazine, Prednisone
OEPA: Vincristine, Etoposide, Prednisone, Adriamycin
R-CEOP: Rituximab, Cyclophosphamide, Epirubicin, Vincristine, Prednisone
RT: Radiotherapy
Figure legends

Figure 1: Chronological overview of Hodgkin lymphoma relapses
Change of clonal relationship is highlighted by different colors. Brown triangles indicate positivity for LMP1/EBER. Unlabeled rectangles indicate morphologically unclassifiable Hodgkin lymphoma cases. Uncolored rectangles indicate PCR analysis failures.

Abbreviations:
DLBCL: diffuse large B-cell lymphoma
IgH: immunoglobulin heavy chain gene
NS: Nodular sclerosing subtype of HL
MC: Mixed cellularity subtype of HL
LD: Lymphocyte depleted subtype of HL

Figure 2: Clonal peaks in (A) clonally related (patient no. 12) and (B) clonally unrelated (patient no. 14) relapsing Hodgkin lymphomas (HL). Inserts illustrate the morphology of the corresponding samples.
A. Clonal peaks at 94 bp in the first PCR run and at 90 bp in the verification PCR run, designed to give shorter products, are seen in the first two graphs from the initial HL sample of patient no. 12. A clonal peak at 95 bp corresponding to a clonally related neoplasm is seen in the third graph form a HL relapse, which occurred seven years later.
B. Clonal peaks at 107, 116 and 134 bp in the corresponding PCR runs are seen in the three graphs from the initial diagnosis, and second and third relapses of patient no. 14, which occurred six and seven years later.

Figure 3: Different immunoglobulin heavy chain fragment lengths and different immunoglobulin heavy chain gene sequences in a first (upper part) and second relapse (lower part) of patient no. 15. A peak at 110 bp is seen in the first relapse, while a peak at 117 bp appears in the second relapse, which occurred two years later.
Sequencing of the amplified IgH gene FR3 region products of the samples is shown below the graphs. Identical base sequences are highlighted in red.
References


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