Pathogenesis, diagnosis, and treatment of composite lymphomas

Ralf Küppers, Ulrich Dührsen, Martin-Leo Hansmann

In rare instances, two distinct lymphomas concurrently occur in a patient. Such composite lymphomas can be combinations of two non-Hodgkin lymphomas or a combination of a non-Hodgkin lymphoma and a Hodgkin’s lymphoma. Composite lymphomas pose a particular diagnostic challenge, and there are currently no agreed standards for treatment. Combined B-cell non-Hodgkin lymphomas are often clonally unrelated. However, in many composite non-Hodgkin lymphomas and Hodgkin’s lymphomas, the tumours are clonally related. In most of these instances, the malignant clones developed separately from a common precursor, usually a germinal centre B cell. This finding suggests a scenario in which the common premalignant precursor had acquired shared transforming events, and the two distinct lymphomas developed from descendants of that precursor after acquiring additional separate transforming events. Findings from molecular studies support this notion. Hence, clonally related composite lymphomas are elegant models to study the multistep transformation process in lymphomagenesis.

Introduction

In the WHO lymphoma classification, 54 different types of B-cell and T-cell lymphomas are distinguished.1 The definition of a particular lymphoma entity is based on the cellular origin of the lymphoma cells, their typical morphological features, histological characteristics of the microenvironment, immunophenotype of tumour cells, and sometimes on specific genetic lesions.2 The distinction of lymphomas is of major clinical relevance because various types of lymphomas can have very different clinical behaviour, and treatment protocols for distinct lymphoma entities vary considerably.

In rare instances, two distinct types of lymphomas occur in the same patient. Such lymphomas are called composite lymphomas. This term was introduced in 1954 by Custer3 and later refined by Kim and colleagues.4 About 1–4% of lymphomas are composite lymphomas.4 Composite lymphomas can be composed of a Hodgkin’s lymphoma and a non-Hodgkin lymphoma or of two distinct non-Hodgkin lymphomas. A few cases of combined classic and nodular lymphocyte predominant Hodgkin’s lymphoma (NHLPHL), the two major subtypes of Hodgkin’s lymphoma, have also been described.5 Composite lymphomas occur concurrently in a patient and mostly together in the same organ. However, sometimes two lymphomas presenting sequentially in a patient are classified as composite lymphomas. If a low-grade (indolent) lymphoma develops into a high-grade (aggressive) lymphoma, this case is not considered to be a composite lymphoma, but a lymphoma transformation. Examples of such instances are the transformation of a chronic lymphocytic leukaemia (CLL) or follicular lymphoma into a diffuse large B-cell lymphoma (DLBCL).6

We review the main aspects for the pathological evaluation of composite lymphomas, and we discuss what is known about their pathogenesis and how composite lymphomas are treated.

Pathology and diagnosis

To establish the diagnosis of composite lymphoma, a biopsy is needed. This biopsy—which is typically a lymph node—has to be investigated with morphological, immunohistochemical, and molecular techniques. The morphological criteria include cytological features of the tumour cells and the bystander cells, and the growth pattern of the lymphoma. In composite lymphomas, morphologically different lymphoma types occur in one lymph node or in different sites of one patient. There can be sharp or diffuse borders or even partial mixtures of infiltrates of different lymphoma types if they occur in the same organ. Immunohistochemical markers are helpful to define the tumour and the bystander cells more precisely and to clarify whether they represent two different lymphoma types. If a lymphoma shows morphological or immunohistochemical aspects of another lymphoma entity—eg, primary mediastinal B-cell lymphoma (PMBCI) with features of Hodgkin’s lymphoma—it is known as a grey-zone lymphoma, and not a composite lymphoma.7,8 Composite lymphomas include a broad range of different lymphoma types. In this section, we describe several relatively common types of composite lymphoma.

DLBCL are a heterogeneous group of aggressive B-cell neoplasias composed of large blasts that can have features of centroblasts or immunoblasts and express B-cell markers such as CD20, CD19, CD79a, and PAX5, and show immunoglobulin κ or λ light-chain restriction.7 In combined DLBCL and Hodgkin’s lymphomas, lymph nodes typically present with one area dominated by the typical histological picture of a DLBCL, and a separate area with a histological picture of classic Hodgkin’s lymphoma, characterised by many small T cells intermingled with macrophages, eosinophilic granulocytes, and large blasts showing features of Hodgkin’s and Reed–Sternberg (HRS) cells, the tumour cells of classic Hodgkin’s lymphoma. This composition is characteristic of a classic Hodgkin’s lymphoma.8 Additionally, the expression of
typical markers of HRS cells—ie, CD30, CD15, weak expression of PAX5, and MUM1—further support the presence of a typical classic Hodgkin’s lymphoma. Figure 1A–B and figure 1C–D are typical examples of composite DLBCL and classic Hodgkin’s lymphomas. Figure 1A and 1C show the DLBCL aspect, figure 1B and 1D show the corresponding Hodgkin’s lymphoma component. In some cases, special immunohistochemical marker constellations seen in non-Hodgkin lymphomas can pose differential diagnostic difficulties. For example, DLBCL, and especially their anaplastic variants, might also partly express CD30.

Follicular lymphoma is the prototypical type of germinal centre B-cell lymphoma. This lymphoma, which can grow in a follicular and in a diffuse pattern, can be found in combination with classic Hodgkin’s lymphoma. The tumour B-cell population of follicular lymphomas is composed of varying amounts of centroblasts and centrocytes, the two types of germinal centre B cells, and hence simulates germinal centre structures. In composite follicular lymphoma and classic Hodgkin’s lymphoma, the typical pattern of classic Hodgkin’s lymphoma is seen in addition to the follicular structures of the follicular lymphoma. Figure 1E–F and figure 1G–H are typical examples of composite lymphomas made up of a follicular lymphoma and a Hodgkin’s lymphoma. Figure 1E shows the follicular lymphoma component, figure 1G shows a pale Hodgkin’s lymphoma area and CD20-positive neoplastic follicles of follicular lymphoma, figure 1F and 1H show the corresponding Hodgkin’s lymphoma component. The HRS cells in the Hodgkin’s lymphoma component show the typical markers. CD30 and CD15 are especially useful to further validate the diagnosis of Hodgkin’s lymphoma. However, the typical composition of a Hodgkin’s lymphoma should be identified. Otherwise, a differential diagnosis of grey-zone lymphoma has to be considered.

CLL is defined by clonal proliferates of small to medium sized CD5-expressing B cells, usually showing proliferation centres in infiltrated lymph nodes. In composite CLL and Hodgkin’s lymphoma, defined areas of the CLL show infiltrates of a Hodgkin’s lymphoma, composed of HRS cells with their characteristic markers and the typical bystander cells. The occurrence of only large blasts with features of HRS cells in a CLL microenvironment does not represent a composite lymphoma. The presence of HRS-like cells without a typical Hodgkin’s lymphoma microenvironment is a relatively frequent occurrence in CLL, and such HRS-like cells are often expanded clones of Epstein–Barr virus (EBV)-infected B cells. Moreover, HRS-like cells can be detected in Richter syndrome, which usually represents a transformation of a CLL into a DLBCL. There is also a Hodgkin’s lymphoma variant of Richter transformation. Again, these instances are not considered to be a composite lymphoma.

In addition to combinations of a Hodgkin’s lymphoma and a non-Hodgkin lymphoma, composite lymphomas can also consist of two distinct types of non-Hodgkin lymphoma occurring concurrently in a patient. Such combination lymphomas include DLBCL with follicular lymphomas, mantle cell lymphoma, and others. In these
cases, the distinct components have to be defined separately by conventional and molecular techniques. Furthermore, combinations between B-cell and T-cell lymphomas such as CLL and anaplastic large-cell lymphomas or peripheral T-cell lymphomas not otherwise specified can occur.14

**Pathogenesis**

**Clonal relations of composite B-cell non-Hodgkin lymphomas**

For an understanding of the pathogenesis of a composite lymphoma, whether the two lymphomas are clonally related or not must be classified. Because lymphomas derive from B or T cells, which carry rearranged antigen receptor genes, the clonal relation of the partners of a composite lymphoma can be elegantly and unequivocally determined with their rearranged immunoglobulin or T-cell receptor (TCR) V genes as clonal markers, because each lymphocyte is equipped with a unique receptor, and the V gene rearrangements remain stable during cellular division.

Lymphomas composed of two B-cell non-Hodgkin lymphomas can encompass nearly all possible combinations, but most often represent combined low-grade lymphomas, particularly mantle cell lymphoma with CLL or follicular lymphoma, or follicular lymphoma and CLL (appendix). More than 50 such cases have been molecularly studied for their clonal relation by immunoglobulin V gene analysis or studies for hallmark chromosomal translocations, particularly t(14;18) for follicular lymphomas and t(11;14) for cases of mantle cell lymphomas. 61% of these types of composite lymphomas consist of two clonally unrelated B-cell malignancies (75% if cases that showed some discrepant findings are disregarded, which involved mantle cell lymphomas with an unclear distinction between associated plasmacytic differentiation or combined plasma cell neoplasia, or which represented low-grade lymphomas with a combined DLBCL as potential early high-grade lymphoma transformations; appendix).

**Clonal relation of combined Hodgkin’s lymphoma and non-Hodgkin lymphoma**

Because Hodgkin’s lymphomas are very distinct in their histopathological appearance from most non-Hodgkin lymphomas, composite lymphomas consisting of a
Hodgkin’s lymphoma and a non-Hodgkin lymphoma have raised particular interest regarding a common or separate origin. However, because of the rarity of HRS cells in the tissue, and to ensure sampling of the two lymphomas separately, the lymphoma cells had to be isolated by microdissection from tissue sections for a reliable analysis. Whole tissue analysis might not be sensitive enough to detect clonal rearrangements in the rare HRS or lymphocyte predominant cells. If a clonal amplification is detected from a whole tissue analysis, it would be unclear whether the rearrangement is carried by the HRS or lymphocyte predominant cells of the Hodgkin’s lymphoma or by non-Hodgkin lymphoma cells present in the Hodgkin’s lymphoma microenvironment.

In most instances (11 of 18 informative cases), the classic Hodgkin’s lymphomas and the non-Hodgkin lymphomas were clonally related (table 1). The non-Hodgkin lymphomas found to be clonally related with classic Hodgkin’s lymphomas included follicular lymphoma, mantle cell lymphoma, DLBCL, and CLL. Additionally, a combination of a cutaneous T-cell lymphoma clonally related to a classic Hodgkin’s lymphoma in a lymph node has been described. This case thus represents a further example of the rare instance in which HRS cells have a T-cell origin.

NLPHL has a tendency to transform into a high grade lymphoma, and although few of these cases have been molecularly analysed in detail, it is generally assumed that a DLBCL developing after a NLPHL represents a high-grade transformation of the NLPHL. However, a composite NLPHL and DLBCL, and a composite NLPHL and T-cell-rich B-cell lymphoma at initial diagnosis have been identified (table 1). In both instances, the lymphomas were clonally related. Moreover, in two combinations of a NLPHL with a classic Hodgkin’s lymphoma, their common origin was shown.

Consecutive cases of two histopathologically distinct lymphomas in one patient are strictly defined as not composite lymphomas. Nevertheless, for such cases, whether these two lymphomas are independent or clonally related is of interest pathogenetically. In eight out of 18 combinations of a Hodgkin’s lymphoma and a non-Hodgkin lymphoma that were diagnosed consecutively, the lymphomas were clonally unrelated (table 2). In these instances, the development of the second lymphoma might have been a chance occurrence.
or promoted by the chemotherapy or radiotherapy that the patient received for treatment of the first lymphoma. In ten consecutive lymphomas, however, the two tumours showed a common clonal origin (table 2).

Three of the clonally related sequential lymphomas were combinations of classic Hodgkin’s lymphoma with primary mediastinal B-cell lymphoma.47,49 This combination of lymphomas occurs relatively frequently.50 Although the common origin of such lymphomas was shown only in the three cases studied so far, many of these sequential lymphomas might be clonally related, considering that several recurrent genetic lesions are common in both types of lymphomas (eg, mutations in TNFAIP3 and SOCS1, amplifications of JAK2 and REL), and that mediastinal grey-zone lymphomas showing features of both classic Hodgkin’s lymphoma and primary mediastinal B-cell lymphoma exist.47,48

Cellular origin of combined Hodgkin’s lymphomas and B-cell non-Hodgkin lymphomas

In more than half of the cases of composite Hodgkin’s lymphoma and non-Hodgkin lymphoma, the two lymphomas share a common origin, and even in consecutive occurrences of a Hodgkin’s lymphoma and a non-Hodgkin lymphoma more than half of the cases were clonally related. Thus, histopathologically very distinct lymphomas can derive from a common precursor. Importantly, as the cellular derivation of HRS cells in classic Hodgkin’s lymphoma has been debated for a long time,36,50 the finding that HRS cell clones in composite lymphomas often share a common origin with a typical mature B-cell lymphoma is a further strong argument for a derivation of HRS cells from mature B cells.15

The analysis of the rearranged IgV genes of the two components of a composite lymphoma provides information not only about their clonal relation but also about the differentiation stage of the cell of origin and the specific relationship between related composite lymphomas. This is based on the unique feature that rearranged IgV genes undergo somatic hypermutation when antigen-activated B cells participate in T-dependent immune responses in histological structures called germinal centres.51 As a result of the stepwise accumulation of somatic V gene mutations during the expansion of germinal centre B-cell clones, they consist of multiple members with both shared and unique mutations. Because somatic hypermutation is restricted to germinal centre B cells, the detection of mutations in IgV genes identifies such cells as germinal centre or post-germinal centre B cells. Importantly, most human B-cell lymphomas are derived from post-germinal centre B cells.39

In most instances of related composite Hodgkin’s lymphoma and B-cell non-Hodgkin lymphoma, the IgV genes were somatically mutated (table 1). Strikingly, in nearly all these cases, the IgV genes showed both shared mutations and mutations present in only one of the two lymphomas. Thus one lymphoma clone is not the direct descendent of the other (in that case, all mutations found in the paternal tumour should be present in the descendent, with perhaps additional mutations in the descendent). The mutation pattern seen in these cases suggests that both lymphomas share a common origin—a mutated germinal centre B cell—from which the two lymphomas then developed independently with decisive steps in the pathogenesis of these lymphomas occurring in the germinal centre microenvironment (figure 2).15,31

A common origin was also noted in four of five instances in which a Hodgkin’s lymphoma and a B-cell non-Hodgkin lymphoma developed consecutively (table 2). Thus, in these consecutive cases, the later lymphoma is not a transformation of the first lymphoma clone but developed separately from a common, presumably premalignant, precursor. This scenario indicates that the premalignant common lymphoma precursor resided in the patient for several years before it finally fully transformed and gave rise to the later occurring lymphoma. In a case of a sequential splenic marginal zone lymphoma and classic Hodgkin’s lymphoma, both lymphomas carried unmutated V-region genes. These lymphomas might derive from a pre-germinal centre B cell, and the HRS cell clone might be a direct descendent of the B-NHL clone. However, also in this instance, the HRS clone could principally derive from a germinal centre B cell, because germinal founder cells already acquire the phenotype of germinal centre B cells, undergo proliferation and become apoptosis-sensitive before somatic hypermutation becomes active.

Genetic lesions in combined Hodgkin’s lymphoma and B-cell non-Hodgkin lymphoma
Clonally related composite lymphomas are intriguing models to study the multistep transformation process in lymphomagenesis. Genetic lesions shared by the related lymphomas are early events that occurred in the common

Figure 2: Scenario for generation of clonally related composite lymphomas of a Hodgkin’s lymphoma and a B-cell 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.
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Hodgkin lymphoma but not in HRS cells. Moreover, detectable by immunohistochemistry in the B-non-mantle cell lymphoma, cyclin D1 expression was one of the cases of composite Hodgkin’s lymphoma and Hodgkin’s lymphoma remains an intriguing question. In what their role was in the pathogenesis of the associated for the B-cell non-Hodgkin lymphoma is without doubt, development of two histopathologically distinct tumours of the follicular lymphoma was also carried by the HRS cells.54 Hence, these are examples of common early genetic lesions in the pathogenesis of composite lymphomas.

Although the pathogenetic role of these translocations for the HRS cell clone after the tumour clone had acquired additional genetic or epigenetic aberrations. Indeed, proto-oncogenes translocated into Ig loci of HRS cells might often be downregulated in the HRS cell clones, because the Ig loci are usually silenced in these cells.6 This is, however, not always the case because in the second composite Hodgkin’s lymphoma and mantle cell lymphoma, the HRS cells expressed cyclin D1, which is not normally detected in HRS cells.25 Thus, here the translocation seems to have a role in aberrant expression of cyclin D1 in HRS cells, and the translocated IgH locus was apparently not silenced.

In a combined classic Hodgkin’s lymphoma and DLBCL, somatic mutations in the TP53 gene were present only in the DLBCL (table 3), representing a genetic lesion in a composite lymphoma that was present only in the B-cell non-Hodgkin lymphoma, and hence a late transforming event (figure 3C).24 The absence of TP53 mutations in the HRS cells of that composite lymphoma seems to fit to the finding that TP53 mutations are rare in HRS cells.6 However, in a combined mantle cell lymphoma and classic Hodgkin’s lymphoma, both lymphomas carried an identical and functionally relevant TP53 point mutation (shown in figure 3D to occur in the germinal centre, but might have happened already in a pre-germinal centre B-

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

<table>
<thead>
<tr>
<th>Type and presence of transforming event</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Classical HL; DLBCL</td>
<td>EBV positive; EBV negative</td>
</tr>
<tr>
<td>Classical HL; follicular lymphoma</td>
<td>t(14;18), BCL2/IgH; t(14;18), BCL2/IgH</td>
</tr>
<tr>
<td>Classical HL; MCL</td>
<td>t(11;14), BCL1/IgH, TP53 deletion and mutation; t(11;14), BCL1/IgH, TP53 deletion and mutation</td>
</tr>
<tr>
<td>Classical HL; MCL25</td>
<td>t(11;14), BCL1/IgH, subclone EBV positive; t(11;14), BCL1/IgH, EBV negative</td>
</tr>
<tr>
<td>Classical HL; NHL</td>
<td>EBV positive; EBV negative</td>
</tr>
<tr>
<td>Classical HL; CLL</td>
<td>EBV positive; EBV negative</td>
</tr>
<tr>
<td>Classical HL; follicular lymphoma</td>
<td>t(14;18), BCL2/IgH; t(14;18), BCL2/IgH</td>
</tr>
<tr>
<td>Classical HL; follicular lymphoma</td>
<td>t(14;18), BCL2/IgH; t(14;18), BCL2/IgH</td>
</tr>
<tr>
<td>Classical HL; folllcular lymphoma</td>
<td>t(14;18), BCL2/IgH; t(14;18), BCL2/IgH</td>
</tr>
<tr>
<td>Classical HL; DLBCL24</td>
<td>TP53 mutations positive; TP53 mutations positive</td>
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HRS cells often express BCL2 in the absence of a BCL2 translocation, which is very rare in HRS cells.26 Hence, the pathogenetic effect of these translocations for the HRS cell clone is debatable.24 Perhaps the translocation events were essential for the development of the HRS cell clone in the early stages of its development, but lost their role in the fully established HRS cell clone after the tumour clone had acquired additional genetic or epigenetic aberrations.

lymphoma precursor, whereas mutations present in only one of the lymphomas are late events that occurred after separation of the two distinct lymphoma precursors. Such separate genetic lesions most likely play a major part in the development of two histopathologically distinct tumours from the common precursor. So far, only a few composite Hodgkin’s lymphomas and B-cell non-Hodgkin lymphomas have been studied for transforming events.

Translocations of the CCND1 (BCL1, cyclin D1) gene to the IgH locus is a hallmark of mantle cell lymphoma, and BCL2/IgH translocations are characteristic for follicular lymphoma.11 These translocations occur in pro-B or pre-B cells as mistakes during V(D)J recombination.51 Thus, it is not surprising that in two instances of clonally related Hodgkin’s lymphoma and mantle cell lymphoma25,54 both lymphomas carried the identical t(11;14) BCL1/IgH translocation (table 3, figure 3). Similarly, in three combinations of classic Hodgkin’s lymphoma and follicular lymphoma, the t(14;18) BCL2/IgH translocation of the follicular lymphoma was also carried by the HRS cell clones (table 3, figure 3A).25,54 Hence, these are examples of common early genetic lesions in the pathogenesis of composite lymphomas.

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cell) and seemed to have acquired independent deletions on the other TP53 allele (figure 3D).25 Hence, in this case the shared TP53 point mutation is an early transforming event in the common lymphoma precursor. However, presence of a further wild-type allele of TP53 in the HRS cells indicated that these deletions happened independently in the two lymphoma clones.

EBV can immortalise human B cells and is found in the HRS cells of about 30% of classic Hodgkin’s lymphomas in developed countries.57 Among several EBV-encoded genes, EBV-positive HRS cells express the latent membrane protein 1 (LMP1) of EBV, which is an oncogene that causes constitutive NFκB activity as a main survival factor for HRS cells.57 For EBV-positive Hodgkin’s lymphomas, in general, at which stage of B cell or lymphoma development EBV infection had occurred is unclear. In five composite lymphomas with confirmed clonal association of the HRS cells with the B-cell non-Hodgkin lymphomas or NLPHL tumour cells, EBV was found in the HRS cells (table 3). In one of these cases only a subclone of the HRS cells (defined by a specific V gene mutation pattern) was infected by EBV. Thus EBV infection was a late event in Hodgkin’s lymphoma pathogenesis and likely occurred in a germinial centre B-cell precursor of the HRS cell clone.

Taken together, although only few transforming events are yet known for composite lymphomas, the findings reported so far support the view that clonally related composite lymphomas develop in a multistep transformation process with common early genetic lesions and distinct later lesions, which define the separation of the lymphoma precursors.

**Composite T-cell and B-cell lymphomas**

Several composite lymphomas encompass a B-cell and a T-cell lymphoma. Various types of B-cell lymphomas, including CLL, NLPHL, DLBCL, and plasma cell neoplasias, have been identified combined with different forms of T-cell non-Hodgkin lymphoma, including angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma, and peripheral T-cell lymphoma, not otherwise specified.66–69 In these cases, the B-cell and T-cell tumour clones clearly derive from separate precursors. The simultaneous occurrence of a B-cell and a T-cell lymphoma (or of two unrelated B-cell non-Hodgkin lymphomas) might be a chance occurrence or linked to an underlying genetic predisposition for lymphoma generation, or an environmental risk factor could be involved.61 Moreover, an immunological effect could have a role. A lymphoma can produce cytokines or other factors that chronically stimulate other lymphocytes, or an immunosuppressive microenvironment in a lymphoma could promote the unrestricted expansion of other lymphocytes, thus increasing the risk of a second lymphoma developing in parallel to the initial malignant clone.

Regarding the pathogenesis of combined B-cell and T-cell lymphomas, AITL is particularly informative. AITL
is a subtype of mature T-cell non-Hodgkin lymphoma with a derivation of the lymphoma cells from follicular T-helper cells. A remarkable feature of AITL is that these T-cell lymphomas frequently show expanded B-cell clones in the lymphoma microenvironment, and in 10% of the cases frank B-cell lymphomas develop in the course of the disease or are already present at diagnosis. The malignant T-cell clone as a transformed germinal centre T-helper cell could produce B-cell stimulatory factors that cause a constant stimulation of B-cells, promoting their malignant transformation. Moreover, as many (although not all) B-cell clones and B-cell tumours in the setting of AITL are EBV positive, the specific microenvironment in AITL might allow the unrestricted expansion of EBV-infected B cells, increasing the risk for the development of an EBV-positive B-cell lymphoma. Finally, mutations in the tumour suppressor gene TET2 have been detected not only in the T-cell tumour clones of AITL but also in some monocytes and haemopoietic precursor cells of the patients. Thus, such TET2 mutations might also be present in the B-cell clones, representing an example of a very early shared genetic lesion occurring in a haemopoietic precursor cell. This genetic lesion would hence contribute to the development of both the T-cell and the B-cell lymphoma, and might explain why patients with AITL frequently develop B-cell lymphomas.

Combinations of lymphomas with histiocytic/dendritic cell sarcomas
It is unusual to see the combined occurrence of a B-cell non-Hodgkin lymphoma with a histiocytic or dendritic cell sarcoma. Although these combinations—which can contain CLL, follicular lymphoma, DLBCL, and splenic marginal zone lymphoma—are not called composite lymphomas, they are relevant to this Review because of potential clonal relationships. Strikingly, molecular studies of such combined lymphomas and sarcomas for rearranged IgV genes or chromosomal translocations (in particular BCL2/IgH translocations in cases of follicular lymphomas) showed that they are indeed often clonally related. Such cases could principally derive from a common, immature haemopoietic precursor, they could represent a dedifferentiation of a B-cell lymphoma to an immature precursor followed by its differentiation into a myeloid or dendritic cell, or they could represent a more direct transdifferentiation. The presence of the same rearranged and somatically mutated IgV genes in the B-cell lymphoma and the sarcoma argues against the first scenario, and the fact that dedifferentiated cells have never been seen in such cases argues against the second. The possibility of a direct transdifferentiation is supported by the finding that, in a mouse model, enforced expression of the myeloid transcription factor CEBPB is sufficient to transdifferentiate B cells into macrophages. This occurrence is accompanied by downregulation of the B-cell master transcription factor PAX5 and increased expression of PU.1, which is expressed at low level in B cells, but highly expressed in macrophages. The mechanisms causing this transdifferentiation are unclear, and mutations inactivating the PAX5 gene have not been identified.

Treatment of patients with composite lymphomas
Dependent on histological subtype, treatment goals for lymphomas vary. Although cure is the goal in chemo-sensitive aggressive lymphomas, such as Hodgkin’s lymphoma and DLBCL, a palliative approach with an initial watch-and-wait strategy is frequently used in CLL, follicular lymphoma, and other indolent lymphomas which, although incurable, have a natural history spanning years or decades. Despite increasingly intense therapies, the outcome of patients with mantle cell lymphoma or T-cell non-Hodgkin lymphoma remains unsatisfactory.

Irrespective of histology, all present first-line chemotherapy protocols presently available are based on alkylating agents. In CD20-positive B-cell lymphomas, these agents are combined with antibodies directed against the CD20 surface receptor. In indolent lymphomas, six treatment cycles with bendamustine and rituximab induce remissions in 90% of patients. Time to next treatment can be prolonged by antibody maintenance therapy. In aggressive lymphomas, alkylating agents are combined with anthracyclines, glucocorticoids, and other agents in complex protocols. In DLBCL, about two-thirds of patients are cured after six to eight cycles of the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), which is regarded as the standard of care in all disease stages. In CD20-negative classic Hodgkin’s lymphoma, treatment duration and intensity are tailored to tumour mass. In early stages, two to four cycles of the ABVD regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) are followed by involved-field radiotherapy, whereas more advanced stages are treated with six to eight cycles of ABVD or six cycles of the more intense BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). With this approach, cure rates of 90% are achieved in all stages. Relapses of DLBCL and Hodgkin’s lymphoma can be cured in some patients by alkylator-based high-dose therapy with autologous blood stem-cell transplantation, which is also an option for indolent lymphomas with short remission duration. Allogeneic transplantation can be of use in patients who do not respond to high-dose therapy.

In composite lymphomas, the overall therapeutic strategy needs to consider both disease components. In view of their rarity and heterogeneity, reliable data for the natural history and the most appropriate treatment are scarce. The existing published work is largely confined to case reports that highlight the biological features with little or no information about disease course or therapy. Nevertheless, the available data suggest that the two or
more components of a composite lymphoma behave similarly to the respective entities alone—ie, Hodgkin’s lymphoma in a composite lymphoma seems to follow a similar course as Hodgkin’s lymphoma alone, and CLL in such a lymphoma behaves like CLL in general.

The possibility of consecutive development of different lymphoma subtypes underscores the importance of repeat biopsies at disease recurrence. In Hodgkin’s lymphoma, 0.7% of presumed relapses proved to be secondary non-Hodgkin lymphomas, most frequently aggressive B-cell lymphomas. When different lymphomas develop sequentially, each disease should be treated according to its own principles. Since knowledge of the clinical behaviour of sequentially developing lymphomas is scarce, this should preferably be done within the context of a prospective clinical trial. When the interval between the first and second lymphoma was short and treatment of the first lymphoma was intense, a first-line approach to the second lymphoma might not be appropriate because its initiating cells were probably already present at first treatment and proved resistant to it. There are no data, however, to support the superiority of a different approach.

Simultaneous presentation of both components of a composite lymphoma poses a greater challenge. If findings from imaging studies show disease manifestations at various locations, the exact stage of each part of the lymphoma can often not be determined. Since stage can affect type and intensity of therapy, all manifestations that cannot unambiguously be assigned to a component of the disease should be attributed to the lymphoma with the less favourable prognosis. This component will also determine the therapeutic strategy. When Hodgkin’s lymphoma is combined with an indolent B-cell lymphoma, treatment should follow the principles of Hodgkin’s lymphoma, with the addition of an anti-CD20 antibody helping to reduce the indolent component. If Hodgkin’s lymphoma is concurrently diagnosed with DLBCL, treatment strategies for the DLBCL have been shown to induce complete remissions of both disease components; in localised stages, radiotherapy can be added to provide adequate treatment for Hodgkin’s lymphoma. Composite B-cell lymphomas have most frequently been treated with the R-CHOP regimen, as in cases of mantle cell lymphomas concurrently diagnosed with follicular lymphoma or DLBCL. When a T-cell lymphoma accompanies a treatment-requiring B-cell lymphoma, an anti-CD20 antibody-containing protocol with good activity in both entities should be selected. Not unexpectedly, the outcome is largely determined by the T-cell component.

Although present treatment protocols for different lymphomas do differ from one another, the differences are often small and sometimes related to historical rather than medical developments. Applying the above rules, adequate treatment can be delivered to most patients with composite lymphomas. With the advent of targeted, more specific therapies, the situation might become more complex. New drugs with a more restricted mechanism of action are likely to change the therapeutic algorithm for composite lymphomas.

Conclusions
The co-occurrence of two unrelated lymphomas could be a chance occurrence, but germline polymorphisms that confer an increased risk for lymphoma development could contribute to the development of unrelated composite lymphomas. The idea that genetic predispositions may cause an increased risk for both Hodgkin’s lymphoma and non-Hodgkin lymphoma is indeed supported by findings from epidemiological studies. Additionally, environmental factors, including chronic viral infections or an impaired function of the immune system to control unrestricted proliferation of transformed lymphocytes, might play a part in the development of two separate lymphomas in a patient.

In most instances of related composite lymphomas, the common precursor was a germinal centre B cell, which further supports the indications that most human B-cell lymphomas develop from these B cells. Even in instances where a Hodgkin’s lymphoma and a related non-Hodgkin lymphoma developed consecutively, the one lymphoma is typically not a transformation from the other lymphoma, but both lymphomas developed in parallel from a common pre-malignant precursor. This parallel development (as opposed to a transformation) indicates that classic Hodgkin’s lymphoma and B-cell non-Hodgkin lymphoma have in crucial aspects distinct pathogenetic mechanisms, so that a fully transformed HRS cell clone cannot transform into a B-cell

Search strategy and selection criteria
We searched PubMed for references published between Jan 1, 1954, and the Jan 31, 2014, in English with the terms “composite lymphoma”, “lymphoma combination”, “histiocytic dendritic cell sarcoma and lymphoma”, “mantle cell lymphoma and chronic lymphocytic lymphoma”, “mantle cell lymphoma and follicular lymphoma”, “follicular lymphoma and chronic lymphocytic lymphoma”, “B and T-cell lymphoma”, and “Hodgkin and non-Hodgkin lymphoma”. We also considered citations within the references found by the PubMed search. For the discussion about the clonal relation between Hodgkin’s lymphoma and non-Hodgkin lymphoma, we only considered studies in which at least the Hodgkin’s lymphoma tumour cells were microdissected for molecular analysis because with whole tissue approaches, cellular contamination by non-Hodgkin lymphoma cells in the Hodgkin’s lymphoma microenvironment and/or insufficient sensitivity to detect genes from the rare HRS or lymphocyte predominant cells is a severe problem.
non-Hodgkin lymphoma, and vice versa, even though both lymphoma clones share some genetic lesions. In concurrent related lymphomas, the parallel multitope development took place over the same time, resulting in the parallel appearance of the two lymphomas. However, in consecutive cases, the premalignant precursor of the later occurring lymphoma apparently resided in the patient for several years before it finally underwent full malignant transformation. Alternatively, malignant transformation of the second lymphoma might have occurred earlier, but the lymphoma was controlled (eg, by the immune system) for several years, before its control failed and it became clinically evident.

The development of clonally related, but phenotypically very distinct lymphomas (eg, composite classic Hodgkin’s lymphoma and B-non-Hodgkin lymphoma) from a common precursor exemplifies the plasticity of lymphocytes, particularly when lymphomas are found in combination with sarcomas. This plasticity is linked to the fact that a small number of master transcription factors define the identity of cells of the immune system; therefore, alterations of a few factors are sufficient to cause very different lymphoid identities and phenotypes. With the availability of whole genome sequencing methods, we now have tools to clarify whether pre-disposing germline alterations favour the development of unrelated composite lymphomas, how shared and distinct transforming events cause the development of clonally related composite lymphomas, and whether particular genetic lesions lead to the transdifferentiation of a B-cell lymphoma into a histiocytic or dendritic cell sarcoma.

Contributors
All three authors searched the literature, interpreted the data, and each wrote parts of the manuscript. RK designed the study, and M-LH provided the immunohistopathological pictures. UD wrote about the treatment of composite lymphomas. All three authors approved the final submitted version.

Declaration of interests
UD received research funding and honoraria from Amgen and Roche Pharma AG. RK and M-LH declare that they have no competing interests.

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