

Pathobiology and treatment of Richter's transformation

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INTRODUCTION — Richter's transformation (RT, Richter's syndrome) was first described in 1928 by Maurice Richter as the development of an aggressive large-cell lymphoma in the setting of underlying chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Although diffuse large B cell lymphoma is the most common histology seen in patients with RT [1], Hodgkin lymphoma [2] and T cell lymphomas [3] have also been reported less commonly. The clinical features, pathogenesis, and treatment of RT will be discussed here.

Evolution to a component of B-cell prolymphocytic leukemia (B-PLL) during the natural history of relapsed CLL/SLL is also common, but is not usually included under the rubric of RT. (See "[Staging and prognosis of chronic lymphocytic leukemia](#)", section on 'Prolymphocytoid transformation'.)

INCIDENCE AND CLINICAL FEATURES

Incidence — The incidence of RT from CLL/SLL to diffuse large B cell lymphoma has been variously estimated at 2 to 9 percent [1,4-7], making it less common than histologic transformation of other low-grade mature B cell malignancies ([picture 1](#)). The median time from the diagnosis of CLL/SLL to transformation has been in the range of two to four years [4,5,8]. For example, a series of 185 consecutive, previously untreated patients with CLL followed for a median of 47 months identified RT in 17 cases (9 percent) at a median of 23 months from diagnosis [7]. This group took an aggressive approach to repeat biopsy, which may explain the high rate of RT. In addition to those transforming to DLBCL, an additional 0.4 percent of patients will transform to Hodgkin lymphoma [9]. (See "[Pathobiology and treatment of histologic transformation in the indolent non-Hodgkin lymphomas](#)", section on 'HT in follicular lymphoma'.)

Clinical features — The onset of RT is heralded by sudden clinical deterioration, characterized by a marked increase in lymphadenopathy at one or more sites (often abdominal), splenomegaly, and worsening "B" symptoms (ie, fever, night sweats, weight loss). The serum level of lactate dehydrogenase (LDH) is elevated in 50 to 80 percent of patients with RT compared with 8 percent of CLL patients [5,8,10].

Anemia with a hemoglobin <11 g/dL is seen in about 50 percent of cases, and thrombocytopenia with a platelet count <100,000/microL in 43 percent [10]. Symptoms are similar in the Hodgkin lymphoma variant. The clinical course of RT is rapidly progressive, with a median survival of 5 to 8 months [1,5,11-13].

Risk factors — Risk factors for the development of RT remain poorly defined.

In a review of the M D Anderson experience between 1975 and 2005, RT occurred in 148 of 3986 patients with CLL (3.7 percent) [10]. In an earlier report of their experience, clinical features associated with RT included [5]:

- Elevated serum lactate dehydrogenase — 82 percent
- Progressive lymphadenopathy — 64 percent
- Systemic symptoms — 59 percent
- Monoclonal gammopathy — 44 percent
- Extranodal involvement — 41 percent

No clinical, chromosomal, or treatment groups were significantly associated with RT in this study. In a subsequent review of patients seen between 1992 and 2002, the incidence of RT was 5 percent overall, and was as high as 10 to 13 percent in those who had received three or more previous treatments [1].

Other suggested risk factors include the following:

- An increasing number of prior therapies [5] and younger age [14] have both been associated with higher risk of RT.
- One analysis found that advanced Rai stage, hemoglobin <12 g/dL, and elevated LDH and beta-2-microglobulin levels were associated with increased risk of RT [15].
- A prospective cohort study of 185 patients identified lymph nodes >3cm, absence of del 13q14, CD38 expression and usage of IGHV4-39 as risk factors for RT [7]. Another analysis suggested that CLL with IGHV4-39 and stereotyped B cell receptors had a very high risk of RT (69 percent at five years) [16].
- The G allele of a single nucleotide polymorphism (SNP) in the regulatory region of intron 1 of CD38 has been found to increase the upregulation of CD38 in response to IL-2, and this SNP when heterozygous or homozygous has been associated with the development of Richter's syndrome in a modest number of patients [17].

Although immunosuppression related to treatment with [fludarabine](#) has been suggested to promote RT, several studies have found that purine analogue therapy is not a risk factor [5,18,19].

MAKING THE DIAGNOSIS

Imaging — Imaging may be helpful in the initial diagnosis of RT. In one report, 9 of 29 patients suspected of having RT had a positive gallium scan; of those, seven had RT on biopsy and two had fungal infections [20]. A second study of 37 patients using PET, in which a standardized uptake value (SUV) >5 was considered suggestive of RT, found that 10 of 11 patients with RT were correctly identified by PET, with one patient missed; however, nine additional patients had false positive PET results [21]. (See "[Evaluation, staging, and prognosis of non-Hodgkin lymphoma](#)", section on 'PET scanning'.)

Biopsy — Biopsy of a likely site of transformation, usually a site of enlarging lymphadenopathy, is required to establish the diagnosis ([picture 1](#)). While biopsy remains necessary to establish the diagnosis, imaging, as above, may provide guidance on the choice of biopsy site.

Bone marrow — The malignant cells of RT can occasionally be seen in the bone marrow and only very rarely in the peripheral blood. An attempt was made to predict the presence of RT without a lymph node biopsy by studying bone marrow in a group of 78 randomly selected patients with CLL and 29 patients with histologically-confirmed RT [22]. The presence of >7 percent "large cells" (greatest nuclear dimension more than twice that of a normal lymphocyte) in the bone marrow along with a serum beta-2 microglobulin level >5 mg/L in a patient with CLL predicted for a clinical outcome similar to that of patients with RT (median survival nine months). However, these findings could be explained by advanced progressive CLL even in the absence of RT, and therefore serve more as prognostic markers than as necessary predictors of RT.

Histology — The histologic diagnosis in patients with RT is usually that of a diffuse large B-cell lymphoma [10]. In some cases, the CLL and RT cells had a common origin [10,23], while in others the RT cells apparently arose de novo [24]. (See "[Clinical manifestations, pathologic features, and diagnosis of diffuse large B cell lymphoma](#)", section on 'Clinical presentation'.)

PATHOGENESIS — As noted above, the diffuse large B cell lymphoma (DLBCL) clone may arise from the underlying CLL/SLL, may represent evolution from a biclonal phenotype in the CLL/SLL, or may represent a new clone. Many cases have been investigated using analysis of immunoglobulin isotypes [8], immunoglobulin heavy chain gene rearrangements [1,6,25], and chromosomal abnormalities. Although DLBCL arising by transformation of other low-grade lymphomas is almost always clonally related, an older review of the literature found that DLBCL arises by clear clonal evolution from underlying CLL/SLL only about 60 percent of the time [26]. Some of the other cases in this study were of ambiguous origin, however, and more recent studies have suggested that the DLBCL and CLL more commonly have

clonal origins, as much as 90 to 100 percent of the time [5,27]. Significant differences in immunophenotype, for example loss of CD5 or CD23, can occur in the RT regardless of clonal relationship with the underlying CLL [28].

The acquisition of new cytogenetic abnormalities is common in the evolution of CLL/SLL even without histologic transformation [27], but is also associated with RT. Marked aneuploidy has been reported in RT arising from previously untreated CLL with a normal or near-normal karyotype [29,30]. A study using comparative genomic hybridization (CGH) in CLL found on average 1.1 genomic imbalances in early stage CLL, 2.1 in progressive CLL, and 4.7 in RT [27]. The imbalances previously present in the CLL were maintained in the RT [27], again suggesting clonal origin.

FISH studies of microdissected large cells in the bone marrow of CLL patients with RT have found a higher incidence of loss of 11q (ATM) and 17p (p53), as well as chromosome 20, in the larger DLBCL-like cells than in the adjacent small CLL cells [31]. Deletion of 11q has been reported more commonly in RT than CLL, in one study in all three cases of RT, as compared with 13 of 62 patients with CLL/SLL (21 percent) [32]. Other specific abnormalities associated with RT include acquisition of trisomy 12 [33], and losses of 8p and chromosome 9 [27].

Lack of somatic hypermutation of the immunoglobulin heavy chain variable region (IgVH) in CLL is associated with progressive disease and a poor prognosis. Not surprisingly, a few small studies have found that most cases of RT appear to arise from these IgVH unmutated CLLs [34,35]. One study found that 18 of 23 (78 percent) cases of DLBCL RT demonstrated clonality with the underlying CLL by IgVH sequence analysis, and of these, 73 percent of the underlying CLLs had unmutated IgVH genes [28]. Interestingly, four of the five RTs that were not clonal with the underlying CLL had mutated IgVH genes [28]. (See "[Staging and prognosis of chronic lymphocytic leukemia](#)", section on '[Defining good and poor prognostic groups](#)'.)

The possible exception to this is the Hodgkin lymphoma variant of RT; Hodgkin lymphoma is usually thought to arise from germinal center or post-germinal center B cells, which are therefore expected to have undergone somatic hypermutation [36]. In one study of four cases of Hodgkin's variant RT, three lacked expression of ZAP-70, which usually correlates with the presence of somatic hypermutation [36]. Five of six cases of CLL associated with Hodgkin variant RT were found to have mutated IgVH genes [28].

However, some evidence suggests that cases of RT acquire the capacity for somatic hypermutation similar to many cases of DLBCL. RT cases showed higher levels of activation-induced cytidine deaminase (AID) and hypermutation of c-MYC, PAX-5 and RhoH, which were not seen in their predecessor CLLs or CLLs that did not

transform [35,37]. Microsatellite instability (MSI) has also been identified in four of nine cases of RT as compared with none of 10 cases of CLL [38]. No evidence of mutation of hMLH1 or hMSH2 has been found, but the hMLH1 promoter was found to be hypermethylated in those cases with MSI [38].

Mutations of individual tumor-suppressor and cell cycle regulatory genes have also been reported to be associated with RT. P53 mutations are common, detected in three of seven RT tumors as compared with 6 of 40 CLLs [39]. Mutations of INK4a/ARF, a possible upstream regulator of p53 activity, have been found in 29 percent of RT cases as compared with 4 percent of CLLs [40] and are often present when p53 mutation is absent [41]. Together these mutations are present in about 60 percent of RT [1].

The cell cycle inhibitor p21 has also been found to be overexpressed in 3 of 7 RTs as compared with 3 of 15 CLLs [42]; although most CLLs had strong p27 reactivity and no expression of the retinoblastoma (Rb) protein, the RT tumors had no p27 expression and high expression of Rb [42]. These data suggest that dysregulation of the cell cycle in RT may have a different pattern than that seen in CLL, but whether or not these mutations are truly causative remains unclear.

The Epstein-Barr Virus (EBV) has been intermittently implicated in the pathogenesis of RT. The largest pathologic study from the Mayo Clinic found that 4 of 25 (16 percent) patients with DLBCL RT had evidence of EBV in the DLBCL by latent membrane protein (LMP) expression or EBV DNA or RNA [43]. Two other studies found EBV in 5 of 24 cases using similar criteria [10,44]. Although the pathogenic role of the virus is unclear, evidence for its involvement is probably greatest in the Hodgkin lymphoma variant of RT, in which EBV can be found in the RS cells in a majority of the limited reported cases [1,10].

TREATMENT AND PROGNOSTIC FEATURES

Prognosis — Historically, RT has been associated with a dismal prognosis, with median survivals of five to eight months [1]. In the largest reported series of 148 patients with biopsy-proven RT, of whom 135 received therapy and 130 were assessable, the overall response rate to a variety of regimens was 39 percent, with 12 percent complete responses [10].

Although not statistically significant, there appeared to be an improvement in response rate with the addition of rituximab, from 34 percent to 47 percent. The median failure-free and overall survivals were seven and eight months, respectively. On multivariate analysis, factors that independently correlated with shorter survival included [10]:

- Platelet count <100,000/microL
- ECOG (Zubrod) performance status >1 ([table 1](#))
- Tumor size >5 cm
- More than 1 prior treatment
- Lactate dehydrogenase level >1.5 times the upper limit of normal

Median survivals for those with zero to one, two, three, or four to five of these adverse factors were 1.12, 0.90, 0.33, and 0.14 years, respectively.

Treatment — Treatment of RT has generally relied on combination chemotherapy such as that used for aggressive non-Hodgkin lymphomas or acute lymphoblastic leukemias, with overall response rates ranging from 5 to 40 percent [[1,45-47](#)]. In three reports from M D Anderson, median survival duration was 8 to 10 months despite intensive multiagent chemotherapy (eg, hyper-CVXD, CHOP, ESHAP, MINE, FCR), with or without the addition of [rituximab](#), with complete and overall response rates of 14 and 39 percent, respectively [[10](#)], and a rate of early death as high as 20 percent [[45,46](#)]. The overall response rate was higher when rituximab was added to the chemotherapy regimen (47 versus 34 percent), although this difference did not attain statistical significance. A combination chemotherapy regimen containing [oxaliplatin](#), [fludarabine](#), [cytarabine](#) and rituximab (OFAR) has been developed for RT and fludarabine-refractory CLL. Twenty patients with RT were treated, with a 50 percent response rate and a median response duration of 10 months. Unfortunately however the six-month overall survival rate of this group was still only 59 percent [[48](#)].

Improved therapeutic options are clearly needed. Yttrium-90 [ibritumomab](#) tiuxetan has been tested in seven patients with no clinical responses and significant hematologic toxicity [[47](#)]. The role of radiation therapy is generally limited to palliation, since RT is rarely a localized disease.

Hodgkin lymphoma variant — For the Hodgkin lymphoma (HL) variant of RT, data on therapy are limited. The majority of patients have high-risk features if prognostic models for de novo HL are applied [[9](#)]. Disease response and clinical outcomes are worse than in de novo HL but better than in DLBCL RT [[2,9](#)]. The majority of patients have received combination chemotherapy targeted at HL, including ABVD, MOPP, or CVPP, with a 44 percent response rate in the largest series and some long-term survivors [[9](#)]. Aggressive NHL regimens such as those used for DLBCL RT have also been tried, with fewer reported successes [[9](#)]. (See "[Initial treatment of advanced \(stage III-IV\) Hodgkin lymphoma](#)".)

Hematopoietic cell transplantation — Given the poor efficacy of combination chemotherapy, short duration of remission, and poor overall survival of RT, allogeneic hematopoietic cell transplantation [HCT] has been explored as a

therapeutic option. However, data remain very limited. An initial study of eight patients, five of whom were in resistant relapse and three in sensitive relapse, found that three subjects (38 percent) died in the first 30 days, while three were alive and in remission at 1, 4, and 5.5 years; two of the three survivors had received nonmyeloablative conditioning [49].

The largest reported HCT series of 20 patients (3 autologous, 17 allogeneic of which 15 were nonmyeloablative) found the following estimated three-year overall survivals [10]:

- 75 percent for patients who underwent allogeneic HCT following an objective response to prior chemotherapy (ie, attainment of CR, CRu, or PR)
- 27 percent for patients with an objective response to chemotherapy who did not have a consolidative HCT
- 21 percent for patients with relapsed or refractory RT who underwent allogeneic HCT as salvage therapy

Four of the 17 patients undergoing allogeneic HCT in this report remained in complete remission, with progression-free survivals between one and six years. Clearly, survival was best in those patients with chemosensitive disease who underwent allogeneic HCT while in first complete remission.

SUMMARY AND RECOMMENDATIONS

Clinical presentation — Richter's transformation (RT) should be suspected in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) who develop rapidly progressive lymphadenopathy or extranodal sites of disease, systemic symptoms, or elevated levels of serum lactate dehydrogenase. (See ['Incidence and clinical features'](#) above.)

Diagnosis — Biopsy is required to confirm the diagnosis, and usually shows a histologic pattern consistent with diffuse large B-cell lymphoma (DLBCL). Occasional patients may have a histologic picture consistent with Hodgkin lymphoma. (See ['Making the diagnosis'](#) above.)

Treatment

- The prognosis and outcome are historically poor for RT and the disease is invariably fatal if left untreated.
- For patients with the DLBCL histologic pattern of RT, we recommend the use of combination chemotherapy as employed for aggressive lymphoma, combined with [rituximab](#) (eg, CHOP-R, [table 2](#)). (**Grade 1C**). (See ['Treatment'](#) above and ["Initial treatment of diffuse large B cell lymphoma"](#).)

- Since complete remissions after chemotherapy are short-lived, and long-term survivors have been reported following allogeneic hematopoietic cell transplantation (HCT), we suggest the use of nonmyeloablative allogeneic HCT when first remission has been achieved in patients who are transplant candidates. (**Grade 2B**). (See '[Hematopoietic cell transplantation](#)' above.)
- For patients with the Hodgkin lymphoma (HL) variant of RT, data are very limited; we suggest the use of combination chemotherapy regimens employed in patients with advanced stage HL (eg, ABVD). (**Grade 2C**). (See '[Hodgkin lymphoma variant](#)' above and "[Initial treatment of advanced \(stage III-IV\) Hodgkin lymphoma](#)".)
- Given the limited data on treatment outcomes for RT, all patients with RT are best advised to enroll in an appropriately designed clinical trial.

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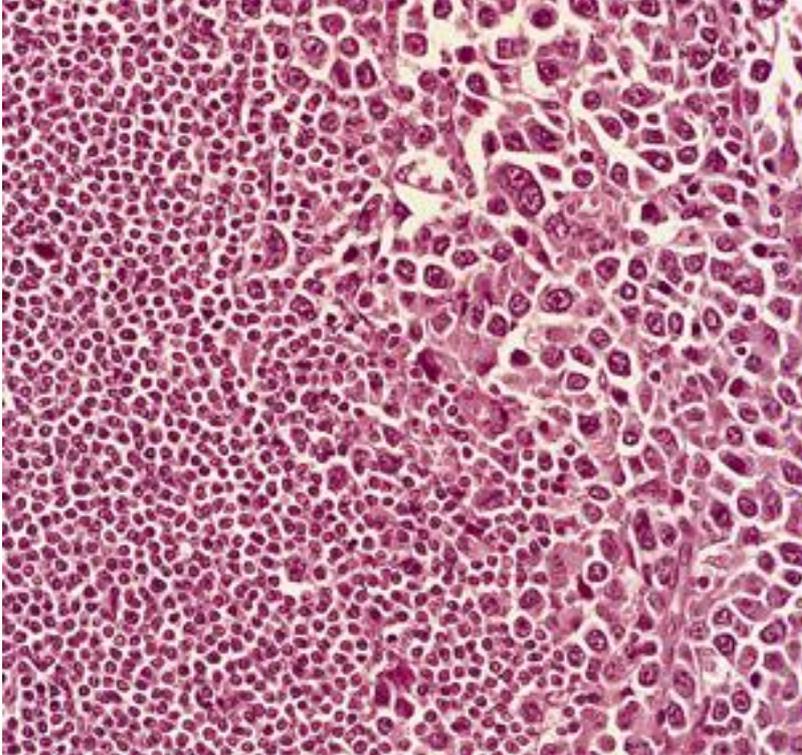
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GRAPHICS: Richter's transformation



Lymph node from a patient with chronic lymphocytic leukemia (B-cell CLL) undergoing Richter's transformation. The monotonous infiltrate of small lymphocytes on the left side, representing the pre-existing B-cell CLL, contrasts with the large B-cells on the right, representing transformation to a diffuse large B-cell lymphoma. *From Warnke, RA, Weiss, LM, Chan, JK, Cleary, ML, Dorfman, RF. Tumors of the lymph nodes and spleen. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 14, 1995, Washington, DC. Armed Forces Institute of Pathology.*

Eastern cooperative oncology group (ECOG, Zubrod) performance scale

Performance status	Definition
0	Fully active; no performance restrictions
1	Strenuous physical activity restricted; fully ambulatory and able to carry out light work
2	Capable of all selfcare but unable to carry out any work activities. Up and about >50 percent of waking hours
3	Capable of only limited selfcare; confined to bed or chair >50 percent of waking hours
4	Completely disabled; cannot carry out any selfcare; totally confined to bed or chair

CHOP chemotherapy for non-Hodgkin's lymphoma

CHOP-21 chemotherapy consists of four agents: Cyclophosphamide (Cytoxan), Doxorubicin (Adriamycin, **H**ydroxydaunomycin), Vincristine (**O**ncovin), and **P**rednisone. One complete course is given every 21 days. Full treatment usually consists of six to eight such courses.

Drug	Dose and Route*	Given on day(s)
Cyclophosphamide	750 mg/m ² IV	day 1
Doxorubicin	50 mg/m ² IV	day 1
Vincristine	1.4 mg/m ² IV•	day 1
Prednisone	100 mg/day PO	days 1 through 5

Major CHOP variants include:

CHOP-14, which uses the same four agents and doses as in CHOP-21 (above), but is given every 14 days. In CHOP-14, filgrastim (G-CSF) is started on day 4 and is continued until day 13.

CNOP, in which Doxorubicin is replaced by Mitoxantrone (**N**ovantrone, 10 mg/m² IV, day 1).

CHOPE/CHOEP, in which Etoposide (100 mg/m² PO) is also given on days 1 to 3. CHOPE/CHEOP can be given every 21 days, or given every 14 days along with G-CSF.

CHOP-BLEO (CHOP-B), in which Bleomycin (10 units/m² IM) is also given on day 1.

R-CHOP, in which Rituximab (375 mg/m² IV) is also given. In one version (GELA), rituximab, cyclophosphamide, doxorubicin, and vincristine are all given on day 1. In another version (ECOG), rituximab is given on day 1 and the other infusions are given on day 3. In a third version (German Low-Grade Lymphoma Study Group) rituximab is given on day zero.

Low-dose CHOP, consisting of cyclophosphamide 400 mg/m², doxorubicin 25 mg/m², vincristine 1.4 mg/m², and prednisolone 60 mg/m², given every 21 days.

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