

An Approach to Diagnosis of Richter Transformation in Chronic Lymphocytic Leukemia

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Abstract

Richter transformation (RT) is the development of high-grade lymphoma in patients with B-cell chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). CLL/SLL is a heterogenous disease with a highly variable clinical course. Disease progression in patients with CLL continues to occur even in the era of novel therapies. A small percentage of CLL patients will develop aggressive histologic transformation to diffuse large B-cell lymphoma (DLBCL), commonly known as RT. It is known that certain genetic aberrations predispose patients to RT, including mutations in *NOTCH1*, *TP53*, *CDKN2A*, and unmutated *IGHV* somatic mutations. Historically, challenges existed in making a definitive diagnosis of RT. More recently, clonal relationships between the underlying CLL and DLBCL-RT are primarily diagnosed by sequencing immunoglobulin genes. Yet, RT continues to present challenges to health-care providers in managing patients with CLL/SLL, even with novel agents. This article aims to increase advanced practitioner awareness of predictive factors for RT, clinical manifestations, and diagnostic criteria to promote early recognition and intervention. Advanced practitioners need to be cognizant of clinical signs of RT and of diagnostic criteria for an appropriate and rapid diagnosis. In doing so, the advanced practitioner can promote early diagnosis and intervention, which may improve patient outcomes, given the dismal prognosis of RT.

Chronic lymphocytic leukemia (CLL) is a chronic incurable heterogenous B-cell disease with a highly variable clinical course (Ding, 2018; Rosati et al., 2018; Khan et al., 2018). Richter transformation (RT) is defined as a histologic transformation of CLL to an aggressive lymphoma known as diffuse large B-cell lymphoma (DLBCL; Wang & Ding, 2020; Pula et al., 2019). Additionally, the 2008 World Health Organization (WHO) defined RT as the transformation of CLL into a more aggressive lymphoma. Richter transformation occurs

due to dysregulation of signaling pathways of CLL cells (Khan et al., 2018; Kohlhaas et al., 2021).

Based on histologic findings, two main types of RT are identified: DLBCL occurring in 80% to 90% of RT cases and classical Hodgkin lymphoma (Gángó et al., 2022). Gángó and colleagues (2022) also indicate rare instances where transformation to plasmablastic lymphoma may occur.

INCIDENCE

Wang and Ding (2020) suggest that approximately 2% to 10% of CLL patients will develop aggressive histologic transformation to DLBCL, which is known as RT. Wang and Ding (2020) further note that 3% to 25% of patients who are treated with novel agents develop RT. They theorize that *TP53* disruption, genomic disequilibrium, and alterations in BCR signaling, coupled with an increased PD-L1 expression and T-cell consumption, are contributing factors in the development of RT in CLL patients treated with novel targeted agents. Pula and colleagues (2019) propose the increased transformation rate annually in CLL patients may be attributed to some patients having preexisting RT prior to initiation of novel therapies compared with all CLL patients. Historically, prior to novel agents such as the Bruton tyrosine kinase (BTK) inhibitor, ibrutinib (Imbruvica), and B-cell lymphoma 2 (BCL-2) inhibitor venetoclax (Venclexta), the reported transformation rate of RT was 0.5% to 1% per year (Ding, 2018). Pula and colleagues (2019) asserted the incidence of RT occurring in up to 10% of all CLL patients with an annual rate estimated at approximately 0.5% to 1%. Diffuse large B-cell lymphoma accounts for approximately 90% of RT cases, while Hodgkin lymphoma variants are also identified (Al-Sawaf et al., 2021; Gángó et al., 2022; Jamroziak et al., 2015). The incidence of RT for ibrutinib ranges from 0.8% to 8%, while a higher incidence of RT for venetoclax monotherapy was up to 16% (Pula et al., 2019). Median age at diagnosis was 69 years (Wang & Ding, 2020).

Al-Sawaf and colleagues (2021) reported a pooled analysis of clinical, laboratory, and genetic data from the German CLL Study Group (GCLLSG). The reported data included frequency, characteristics, and patient outcomes in those with RT. The authors found that of 2,975 patients with advanced CLL who were reviewed for in-

cidence of RT, 103 (3%) patients developed RT. Kaplan-Meier methodology was used to analyze data from time of initial diagnosis of CLL, initial front-line therapy, or transformation to Richter. Median overall survival after diagnosis of RT was 9 months. Median age at diagnosis was 69 years (Al-Sawaf et al., 2021).

RISK FACTORS

An increased risk of RT is associated with many clinical and molecular factors. Prior treatment with purine analogs has been theorized to contribute to RT, as well as with alemtuzumab (Campath, Lemtrada) therapy. In addition, some biological factors such as enlarged lymph node size \geq 3 cm, absence of deletion 13q14, unmutated *IGHV*, and the expression of ZAP-70 and CD38 in CLL/SLL contribute to increased risk of developing RT (Gángó et al., 2022). Other risk factors for consideration include: (1) advanced Rai stage disease (III–V) or Binet stage C, (2) del(17p), (3) trisomy 12, (4) *NOTCH1*, (5) *c-MYC*, (6) germline genetics, and (7) certain aspects of CLL phase biology (Kohlhaas et al., 2021; Khan et al. 2018). Gángó and colleagues (2022) describe clonal relatedness as the most important prognostic factor in RT as compared with clonally unrelated lymphomas. Clonal relatedness refers to the presence of diverse subpopulations within a tumor that possess uniqueness in their molecular characteristics, growth kinetics, and response to therapy (Gutierrez & Wu, 2019). Clonal relatedness has become more apparent through next-generation sequencing, which allows for identification of subclonal populations within the CLL cells (Gutierrez & Wu, 2019).

ASSOCIATED MOLECULAR FEATURES

Richter transformation that develops in the era of novel agents is commonly associated with adverse molecular aberrations, such as *TP53* disruption (60% to 80%), and generally have poor survival outcomes (Wang & Ding, 2020; Gángó et al., 2022). Other genetic alterations that may contribute to RT include *NOTCH1* (30%) mutation, *CDKN2A* (30%), *MYC* (30%), and generally unmutated somatic hypermutations (Pula et al., 2019; Rosati et al., 2018). Mutations in *NOTCH1* are characterized by trisomy 12 activating *NOTCH1* mutations

(Rosati et al., 2018; Hampel et al., 2020). Gain-of-function *NOTCH1* mutations occur in approximately 30% of CLL patients and lead to prolonged signaling (Arruga et al., 2020). *SF3B1* is commonly associated with non-RT in CLL (Ding, 2018; Khan et al., 2018). Loss of *CDKN2A/B* occurs with or without *MYC* abnormalities. *CDKN2A* gene encodes p16INK4A causing dysregulation of *TP53* (Rosati et al., 2018; Ding, 2018, Chakraborty et al., 2020). *TP53* disruption is most commonly found in clonally-related RT cases (Wang & Ding, 2020; Rosati et al., 2018). Even so, unmutated *IGHV* status usually represents clonally-related RT in CLL (Gángó et al., 2022). Additionally, *c-MYC* activation results from deregulation in signaling by other genetic events (Ding, 2018). Lastly, *BCL2/BCL6* rearrangements are identified in de novo RT (Khan et al., 2018). Trisomy 12 is known to contribute to RT (Abruzzo et al., 2018; Ding, 2018; Wang & Ding, 2020; Rosati et al., 2018).

CLINICAL FEATURES OF RT

Patients with concern for RT will often present with some or all of the B CLL constitutional symptoms including fever, significant fatigue, drench-

Table 1. Clinical Features Suggestive of Richter Transformation

Physical features	Laboratory features
Unexplained fever	Elevated LDH
Weight loss	Anemia
Rapidly enlarging bulky lymph nodes ≥ 3 cm	Thrombocytopenia
Splenomegaly	Hypercalcemia
Shortness of breath	Bone marrow involvement

ing night sweats, and unexplained weight loss (Khan et al., 2018). As clinicians, it is important to recognize that progressive B symptoms may represent suspicion for RT. It is equally important to proceed with a thorough history and physical examination where significantly enlarged lymph nodes (> 3 cm) are generally found. Advanced clinical manifestations in RT are described in Table 1.

DIAGNOSTIC CRITERIA

Patients with CLL who present with unfavorable genetic aberrations on initial presentation are at risk for RT after having received therapy with chemoimmunotherapy and newer agents such as

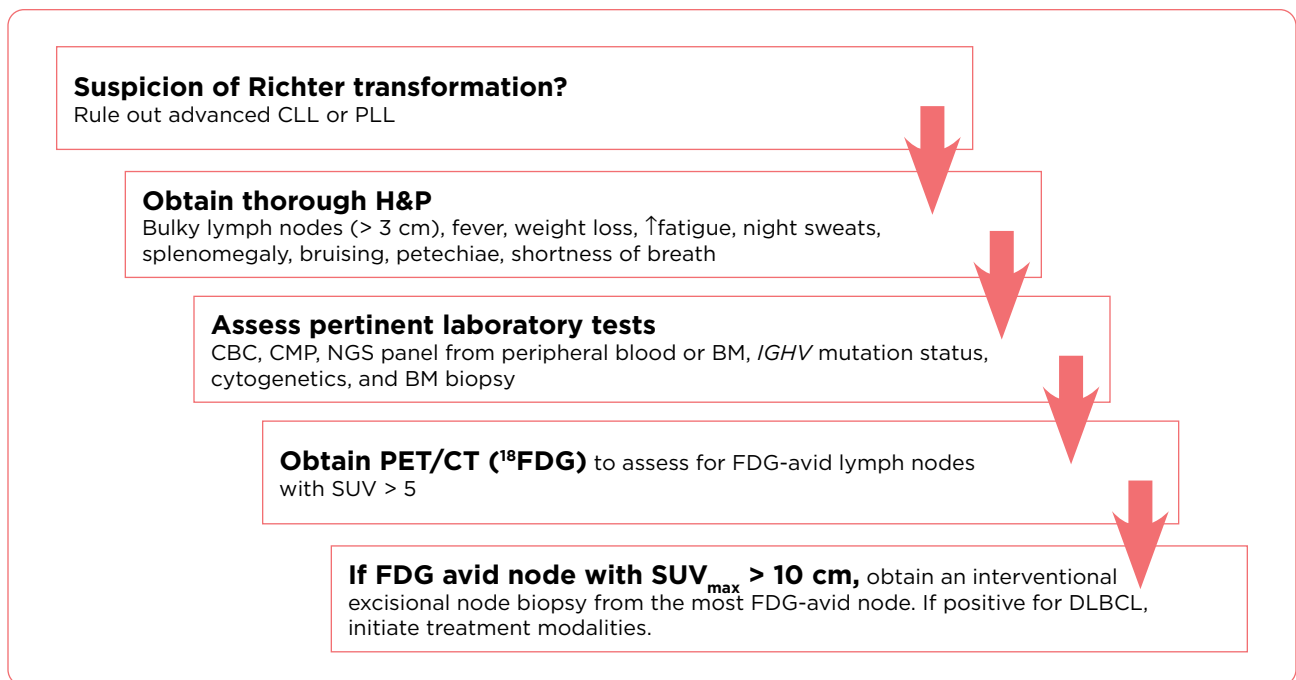


Figure 1. A diagnostic approach to Richter transformation. CLL = chronic lymphocytic leukemia; PLL = prolymphocytic leukemia; H&P = history and physical; CBC = complete blood count; CMP = comprehensive metabolic panel; NGS = next-generation sequencing; BM = bone marrow; *IGHV* = immunoglobulin heavy chain; ^{18}F FDG = ^{18}F -fluorodeoxyglucose; SUV = standardized uptake values.

the BTK inhibitors (Wang & Ding, 2020). The 2018 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines suggest testing of biomarkers on or prior to initial evaluation for RT. When RT is suspected, a series of diagnostic tests are needed to confirm the diagnosis. While flow cytometry of tissue obtained from a fine needle aspiration is suggested by some, the standard approach is a CT-guided interventional excisional biopsy of a specified lymph node (Pula et al., 2019). Whenever suspicion for RT exists, a PET-CT scan is indicated using ^{18}F -fluorodeoxyglucose uptake prior to biopsy to determine the most appropriate nodal biopsy site, preferably with a maximum standardized uptake value ($\text{SUV}_{\text{max}} \geq 10$) (Al-Sawaf et al., 2021; Pula et al., 2019; Wang & Ding, 2020).

Diagnosis of RT is solely confirmed through histopathologic examination of tissue biopsied from a suspected lymph node (Khan et al., 2018; Wang & Ding, 2020; Pula et al., 2019). Diagnostic criteria are summarized in Figure 1. Other etiology such as accelerated CLL and prolymphocytic leukemia may mimic RT and should be considered as differential diagnoses with suspicion of RT (Pula et al., 2019).

CONCLUSION

Richter transformation occurs in approximately 2% to 10% of CLL/SLL patients, particularly in those with prior treatments. The need remains for additional research on the incidence and prevalence of RT in patients treated with novel agents. The presence of certain genetic aberrations in CLL patients has shown to be predictive for transformation to Richter. It is imperative that early clinical evaluation is instituted when suspicion of RT is present. Advanced practitioners have the unique opportunity to impact patient outcomes through early recognition and diagnosis of RT. ●

Disclosure

The author has no conflicts of interest to disclose.

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