



Richter Syndrome: An Aggressive Transformation

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A 71-year-old male patient named M.R. was diagnosed with chronic lymphocytic leukemia (CLL). At the time of diagnosis, M.R. had generalized lymphadenopathy and splenomegaly, which caused him to experience significant abdominal discomfort. M.R. was treated with six cycles of fludarabine, cyclophosphamide, and rituximab (FCR), which is standard first-line chemotherapy, and tolerated this fairly well. His lymphadenopathy quickly resolved and, aside from mild nausea, had no complications from treatment.

Now, three years later, M.R. presented with a four-week history of malaise, fatigue, night sweats, and unintentional weight loss of 15 pounds. He was worried that his CLL was relapsing because his symptoms feel different than when he was diagnosed. He had no other comorbid conditions. On physical examination, M.R. appeared unwell. He had palpable cervical and submandibular lymph nodes (2–3 cm) and bilateral axillary lymphadenopathy measuring 5–6 cm. His white blood cell count was elevated, with an absolute lymphocyte count (ALC) of 32.6×10^9 g/L. At his previous assessment three months prior, his ALC was 10.4×10^9 g/L, indicating a lymphocyte doubling time of less than three months. His hemoglobin and platelets were 9.8 g/dl and 121,000 u/L, respectively, which was significantly lower anemia for M.R. with a stable platelet count. His lactate dehydrogenase (LDH) had always been within normal limits but had now increased to twice the upper limits of normal (590 u/L).

Positron-emission tomography/computed tomography (PET/CT) scan was performed on F-fluorodeoxyglucose and indicated a standardized uptake value (SUV) of 3–4 for the cervical and submandibular nodes and an SUV of

18 and 27 in the axillary nodes. M.R. was referred for an excisional biopsy of one of his axillary nodes. He did not understand why all of these tests were necessary and found the time waiting for appointments very difficult because he was eager to get started on treatment. The biopsy was performed a week later and he was sent home. One week later, M.R.'s oncologist told him that the pathology not only reported his underlying CLL, but also confirmed the presence of a more aggressive, diffuse large B-cell lymphoma (DLBCL), which would require treatment that was different from conventional CLL therapy. M.R. was not surprised by the findings; his doctor had explained that a Richter transformation was a potential outcome. M.R. was eager to start treatment.

A bone marrow biopsy was needed to complete staging, as well as a multi-gated acquisition scan to assess M.R.'s heart function before proceeding with anthracycline-based chemotherapy. He was started on rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP), which is standard chemotherapy for DLBCL. Soon after starting treatment, M.R.'s night sweats ceased, the nodes began to shrink, and his appetite slowly returned. He did not lose any more weight but did experience some nausea from the chemotherapy and mild peripheral neuropathy to his feet. He and his wife were surprised by how much the loss of his hair affected him. He became more withdrawn and isolated with this round of chemotherapy, admitting that, this time, he really "felt like he was sick." He received a total of six cycles and, after completing his chemotherapy, M.R. was scheduled for a repeat PET/CT scan to assess treatment response. He was aware that the prognosis was poor if he had not responded to treatment but

was cautiously optimistic. The previous areas of lymphadenopathy had resolved, but a new retroperitoneal mass was found, measuring 3 x 5 cm, with an SUV of 6.3, which was concerning for disease progression. His advanced age excluded him from stem cell transplantation and he was started on a platinum-based, salvage chemotherapy regimen. M.R. and his wife then began discussions with the nurse and psychosocial clinicians about the uncertainty of their situation and their sense of hopelessness as they begin another round of chemotherapy.

Richter Transformation

CLL is the most commonly diagnosed adult leukemia in the United States and Canada, with the average age at diagnosis being 71.5 years and with men diagnosed slightly more often than women (Jain & O'Brien, 2012). CLL is characterized by an accumulation and proliferation of phenotypically distinct monoclonal B-cell lymphocytes derived from the blood, marrow, or lymph nodes. Despite new understanding about the variable nature of the CLL disease trajectory, CLL is classified as an indolent, low-grade, lymphoproliferative disorder. In about 2%–10% of all cases, patients develop a more aggressive lymphoma known as Richter syndrome or Richter transformation (Parikh, Kay, & Shanafelt, 2014).

First described clinically by Maurice Richter in 1928, the term *Richter syndrome* was applied in the literature 40 years later to a subset of patients with CLL who developed large cell lymphoma (Lortholary et al., 1964). Richter syndrome is the transformation of CLL to an

ONF, 42(2), 200–203.

doi: 10.1188/15.ONF.200-203

aggressive lymphoma (Lortholary et al., 1964). The most common morphologic variant is DLBCL, but Hodgkin lymphoma, prolymphocytic leukemia, and acute leukemia also may be included (Tsimberidou & Keating, 2005). Considered a rare clinical occurrence with a poor clinical outcome, Richter syndrome occurs in 5% of patients with CLL (50 per 1,000), with a risk of transformation of 0.5%–1% per year and a median onset of four years after CLL diagnosis (Tsimberidou et al., 2006). Patients may present at initial diagnosis with concomitant Richter syndrome and CLL (Parikh et al., 2013). Incidence rates are difficult to determine because Richter syndrome is understudied and underreported in the literature, and many cases often are misidentified and treated as progressive CLL rather than a new, more aggressive entity. Greater awareness and greater accuracy in reporting may see incidence rates rise to as high as 16% (compared to 5%) (Rossi et al., 2008). Transformation of CLL to Hodgkin disease is a rare clinical occurrence, with the median time from diagnosis being 4.3 years and a median survival rate of 3.29 years (Parikh et al., 2014). Epstein-Barr infection is more closely linked with the Hodgkin variant Richter transformation than DLBCL (Jain & O'Brien, 2012).

Clinical Presentation

Patients present clinically unwell with rapidly enlarging lymph nodes, fever, weight loss, night sweats, hypercalcemia, and/or elevated LDH, which is not unlike the presentation of aggressive or accelerated cases of CLL (Jain & O'Brien, 2012; Rossi & Gaidano, 2013). Patients also may have extranodal involvement of the kidneys, gastrointestinal tract, lungs, and/or CNS involvement (testes, eyes, sinuses). The usual features of progressive CLL, such as a rapid lymphocyte doubling time, elevated beta-2 microglobulin, and splenomegaly, also may be present in patients with Richter syndrome but have not been found to reliably predict its development (Parikh et al., 2014). Advanced-stage disease (stage III/IV) and nodes larger than 3 cm are the only clinical features associated with an increased risk of developing Richter syndrome and should alert clinicians of possible disease transformation (Maddocks-Christianson et al., 2007; Parikh et al., 2014; Rossi et al., 2008).

Risk Factors

The risk factors for Richter syndrome are unclear. Although the risk of developing a second malignancy is higher in the CLL population, and second lymphoid malignancies occur 3–5 times more often than in the general population, a definitive cause and effect relationship is not yet understood (Maddocks-Christianson et al., 2007). Prior therapy with purine nucleoside analogs has been shown to significantly affect risk, but the impact of conventional chemotherapy is unclear (Parikh et al., 2013). A three-fold increase of Richter syndrome was found in a Mayo Clinic cohort of patients with CLL who subsequently developed biopsy-proven DLBCL ($n = 37$) and who had received a combination of alkylating agents and purine nucleoside analogs; the risk was not higher in patients who had received only single-agent therapy (Parikh et al., 2013). The introduction of new agents in the treatment algorithm for CLL, such as ibrutinib, will mean longer follow-up. Accurate reporting is needed before the impact of new agents on disease transformation is understood.

The presence of Epstein-Barr virus infection in the development of Richter syndrome also has been examined. Several reports of tissue staining for the presence of Epstein-Barr virus infection have found less than 15% of samples were positive for the virus (Ansell, Li, Lloyd, & Phylly, 1999; Rossi et al., 2008; Tsimberidou et al., 2006). Whether the virus plays a causative role in the transformation or whether its presence is simply a manifestation of the patient's underlying immunosuppressed state requires further exploration (Jain & O'Brien, 2012).

Diagnosis

The gold standard for diagnosing Richter syndrome is the excisional biopsy; however, this may not be possible in cases where patients are symptomatic and immediate treatment is required. At minimum, fine-needle aspiration with cytology to confirm the presence of large cells should be performed (Parikh et al., 2014). The use of PET/CT is not routine in the diagnosis and management of CLL, but can play an important role in the diagnosis of transformed disease. Indolent lymphomas are not considered PET avid-sensitive diseases; however,

transformation to an aggressive lymphoma makes tissue highly F-fluorodeoxyglucose avid and can help identify the best node to biopsy for confirmation of the presence of transformation (Falchi et al., 2014). Areas of hypermetabolism on PET/CT may represent other malignancies (i.e., solid tumor), the presence of infection or inflammation, or progressive CLL. Therefore, results should be interpreted cautiously (Conte et al., 2014). A review of 332 patients with CLL and Richter syndrome found an SUV of 5 or greater reliable for identifying an optimal node for biopsy (Falchi et al., 2014). Using an SUV of 5 or greater as a cutoff value, PET/CT has a positive predictive value of only 53% and a negative predictive value of 97%; therefore, in cases with SUV of 5 or greater, performing a biopsy (if clinically possible) to confirm diagnosis is vital (Parikh et al., 2014). Patients with CLL with high LDH were less likely to have SUV values of 5 or greater compared with Richter syndrome patients with high LDH (34% versus 88%, respectively). Lower SUV values (less than 5) also correlated with better survival outcomes (27.6 months versus 7.7 months), whereas cases with higher SUV (10 or greater) correlated with shorter overall survival, regardless of histology (Falchi et al., 2014). A bone marrow biopsy should be performed to complete the staging workup as well as a lumbar puncture if CNS involvement is suspected. Repeat fluorescence in situ hybridization (FISH) studies are helpful at the time of transformation to assess for the presence of new genetic abnormalities (such as trisomy 12, del 11q, and Tp 53 mutation), which have prognostic significance in Richter syndrome (Parikh et al., 2014).

An important feature in Richter syndrome is whether the transformed cell is clonally related to the underlying CLL or whether it represents the development of a new clone. About 75% of cases are clonally related, or evolved from the underlying CLL cell; the remaining cases develop from a new clone (Rossi et al., 2012). IgVH gene sequencing by polymerase chain reaction (PCR) is useful in determining clonality but may not be widely available for clinicians; therefore, other prognostic approaches have been developed. A multivariate analysis identified four important factors predictive of Richter syndrome: the presence of NOTCH1 mutation; IgVH status (mutated); the presence of trisomy 12, del

11q22-23, and TP53 disruption; and CD 38 positivity (30% or greater) (Rossi et al., 2012). The risk of developing Richter syndrome is markedly increased if IgVH and NOTCH1 mutations are present (75% at five years) and rare if neither abnormality is present (0% at five years) (Rossi et al., 2012). Clonally unrelated cases behave similarly to de novo diffuse large-cell lymphoma with similar outcomes and are most commonly IgVH mutated. NOTCH1 mutations are not usually associated with unrelated cases of Richter syndrome (Rossi et al., 2012; Timar et al., 2004). Mutations commonly seen in de novo DLBCL, such as BCL2, BCL6, CD79a, and CD79b, are not generally seen in Richter syndrome (Jain & O'Brien, 2006).

Therapeutic Options

The development of Richter syndrome in patients with CLL necessitates therapeutic intervention because of the rapid nature of disease progression, the presence of extensive tumor burden, and poor performance status. Clinicians must consider prior chemotherapy exposure and the possibility of chemo-refractory disease (caused by TP53 disruption), which may limit treatment options (Tsimberidou et al., 2006). Minimal data exist from clinical trials to assist clinicians (Tsimberidou et al., 2013). Historically, anthracycline-based chemotherapy (i.e., CHOP) has been the most widely used approach because of a favorable toxicity profile, and the addition of rituximab (R-CHOP) has helped to improve response rates (39% overall response rate, 12% complete response) (Maddocks-Christianson et al., 2007). In the salvage setting or for patients with previous anthracycline exposure, more aggressive chemotherapy (including platinum-based regimens) is required. Unfortunately, greater response rates are not seen, and more treatment-related toxicities (such as grade 3/4 neutropenia and thrombocytopenia) negatively affect patients' overall health (Parikh et al., 2014; Tsimberidou et al., 2006, 2013). Although most patients do not achieve an adequate response to proceed to stem cell transplantation, those who do and who have good functional status, and minimal comorbidities should be referred to transplantation as a consolidation strategy (Parikh et al., 2014). The cumulative estimated three-year survival probability (complete or par-

tial response) if transplantation occurs is 75% compared with 21% if stem cell transplantation is used only as salvage therapy in the relapsed, refractory setting (Tsimberidou et al., 2006). The treatment landscape for CLL has changed in recent years, and the role of novel agents, such as ibrutinib, in treating Richter syndrome requires further investigation. Ibrutinib appeared to have single-agent activity in patients (N = 70) with relapsed refractory de novo DLBCL with an overall response rate of 23%; phase III testing is ongoing with ibrutinib in combination therapy (Wilson et al., 2012).

Patient Outcomes

Although overall survival has generally been considered poor, some patients do respond to treatment and achieve long-term remission. The varying prognosis is most closely linked to clonality. Clonally unrelated Richter syndrome has outcomes similar to de novo DLBCL, with median survival rates of 62.5 months compared with just 14.2 months for clonally related cases. A prognostic index has been developed identifying five factors that significantly predict poor outcomes for patients with Richter syndrome: Eastern Cooperative Oncology Group performance status (greater than 1); elevated LDH (greater than 1.5 u/L); platelet count less than 100,000 u/L, tumor size (greater than 5 cm), and number of prior therapies (more than one). Based on the number of risk factors, patients can be stratified

into four groups: low (0–1), low-intermediate (2), intermediate-high (3), and high risk (4–5). Median survival rates were 1.12 years, 0.9, 0.3, and 0.2 months, respectively (Tsimberidou et al., 2006).

Implications for Oncology Nurses

Just as outcomes vary based on the clonality of the disease for patients who develop Richter syndrome, so does the cancer journey. As such, it is important that oncology nurses are equipped with the knowledge to identify and accurately assess patients and understand the emotional and learning needs of this patient population. Patients may struggle to understand this complex, dual diagnosis and the uncertainty of the future. Whenever possible, providing an accurate diagnosis should be attempted because this sometimes lengthy diagnostic period will further heighten the sense of uncertainty and fear for patients. The need to consult clinicians regarding biopsy and diagnosis will mean exposure to more providers, unfamiliar procedures, and an increased passage of time. Nurse intervention is vital at this stage, and patients should be provided with additional information on symptom management and supportive care and be given reassurance and emotional support. For patients who have lived with their CLL diagnosis for years, this new development will change the course of their journey by changing their expectations and understanding of their health situations. Newly diagnosed

Clinical Highlights

Nursing Considerations for Richter Syndrome

- The true incidence of Richter syndrome is unknown, with many cases underreported or misdiagnosed as chronic lymphocytic leukemia (CLL) progression rather than a new entity.
- In patients with stage III/IV CLL who present with bulky, rapidly enlarging lymph nodes, constitutional symptoms, elevated beta-2 microglobulin, elevated lactate dehydrogenase, or hypercalcemia, clinicians should consider Richter syndrome in the differential diagnosis.
- Excisional biopsy is the gold standard for diagnosis and positron-emission tomography/computed tomography may assist in determining the best node to biopsy.
- Clonal evolution of Richter syndrome origin is important in predicting prognosis and patient outcomes.
- Treatment of Richter syndrome differs from CLL treatment and is associated with greater toxicity.
- Patients with Richter syndrome will require additional emotional support and have unique learning needs throughout their journey. Oncology nurses caring for this patient population require more knowledge and awareness to anticipate and address patient concerns.

patients may struggle to understand how the presence of a new, aggressive lymphoma differs from the progression of their CLL.

Case Study Follow-Up

Based on his risk factors, M.R. was classified as having intermediate-high risk Richter syndrome (3 of 5 risk factors) and his life expectancy will likely be shortened by this development. Platinum-based salvage chemotherapy is more toxic and he will likely also require additional supportive care measures such as blood transfusions, hydration, and symptom management while receiving his chemotherapy. M.R. and his wife will continue to require additional emotional support while on therapy and as he transitions to palliative care.

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Key words: chronic lymphocytic leukemia; Richter syndrome; patient education; dual diagnosis

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