CLINICAL VIGNETTE

Richter's Transformation

Logan Pierce, M.D.; Emily Cantor, M.D.; and Ken Kitayama

A 69-year-old man with an 11-year history of chronic lymphocytic leukemia (CLL) currently being treated with ibrutinib was admitted to the medicine service with complaints of shortness of breath, drenching night sweats, and enlarging cervical lymph nodes. Physical exam confirmed cervical lymphadenopathy and pulmonary exam revealed diffuse wheezes and rhonchi. Initial lab findings on admission were significant for a platelet count of 63,000/mcL and an LDH of 1109 IU/L (normal 87-165). He remained afebrile and hemodynamically stable without leukocytosis but was tachycardic to 137 bpm and tachypneic to 22. Chest radiograph on admission was suggestive of worsening paratracheal lymphadenopathy later confirmed by follow-up CT angiography (CTA), which also demonstrated other areas of mediastinal lymphadenopathy as well. CT neck done several days prior to admission showed multiple enlarged cervical lymph nodes bilaterally with the largest dominant node measuring 5.8 cm. On the morning of admission, cervical lymph node biopsy had been obtained to evaluate for progression of CLL. Shortly after the biopsy, he developed shortness of breath and presented to the hospital.

Despite treatment with antibiotics and supportive measures, the patient's dyspnea did not improve. His lymph node biopsy showed diffuse large B-cell lymphoma (DLBCL) with a high proliferation rate (Ki-67 labeling index of 90%), confirming the diagnosis of Richter's Transformation (RT). Further immunohistochemical stains were positive for BCL2 and CD5 co-expression, which are associated with more aggressive lymphomas. A PET-CT was performed to determine the extent of the patient's disease and his treatment options.

Discussion

Richter's Transformation (RT, Richter's Syndrome), first described by Maurice Richter in 1928, is an unfortunate complication of CLL that occurs in approximately 2-9% of patients. It is defined by the development of a new aggressive large B-cell lymphoma that can either be clonally related to the patient's underlying CLL or can arise from a de novo mutation. Typically, this transformation occurs within two to four years after diagnosis of CLL. One study following 185 patients with untreated CLL found 17 cases of RT (9.2%) that occurred anywhere from 0 to 82.4 months (6.8 years) after diagnosis with a median duration of 23 months.[1] However, as our case report illustrates, it is possible for RT to occur much later as well (11 years in this case).

Diagnosis of RT can be difficult for the primary care physician unless clinical suspicion is high, given the infrequency with which it is encountered. Though several studies have attempted to elucidate risk factors for RT, they still remain poorly defined. A 1993 study following 1,374 patients with CLL found RT in 39 patients (2.8%) and identified several clinical features more commonly associated with RT.[2] These features were as follows:

1) Elevated serum lactate dehydrogenase (82%);
2) Progressive lymphadenopathy (64%);
3) Systemic symptoms (59%);
4) Monoclonal gammopathy (44%); and
5) Extranodal involvement (41%).[4]

In addition, the risk of RT was found to increase in proportion to the number of previous therapies attempted for treatment of a patient's CLL. One study noted an overall incidence of RT in 5% of CLL patients but as high as 10-13% in the sub-group of patients who had received three or more prior therapies.[3] Diagnosis can also be suggested by FDG-PET with a standardized uptake value (SUV) >5. Definitive and gold-standard diagnosis of RT is made by biopsy-proven diffuse large B-cell lymphoma taken from the most likely site of transformation, which in this patient was his cervical lymph nodes.

RT is associated with a very poor prognosis. In a 2006 review of 3,986 patients with CLL/SLL who presented to M.D. Anderson between 1975 and 2005, 204 of those patients (5.1%) were found to have had "possible RT." Another 148 patients (3.7%) had biopsy-proven RT.[4] The median survival in patients with biopsy-proven RT was 8 months (95% CI, 6 to 10 months). This study is particularly interesting because not only does it calculate the incidence of RT in CLL it also identifies five statistically significant independent prognostic factors for decreased overall survival, which are as follows:

1) ECOG (Zubrod) performance status > 1 (RR 2.02, p = 0.006);
2) LDH > 1.5x upper limit of normal (RR 1.82, p = 0.003);
3) Platelet count < 100,000 (RR 1.69, p = 0.012);
4) Tumor size > 5 cm (RR 1.61, p = 0.022); and
5) More than one prior therapy (RR = 1.62, p = 0.024).

Based on these data, a scoring system was developed whereby a patient is given one point for each additional risk factor, summing them to determine an 'RT score'. Lower scores are associated with longer survival. In this study, patients with

scores of 0-1, 2, 3, and 4-5, median survivals were 13.4, 10.8, 4.0, and 1.7 months, respectively.

Despite the generally poor prognosis, it is nonetheless reasonable to attempt treatment in most patients with RT who are amenable to it, especially those with a lower RT score. In the 2006 study done at M.D. Anderson, the overall response rate for patients with RT treated with chemotherapy alone was 39%. Complete remission was noted in 12-14% and 25% had a partial remission. Stem Cell Transplantation (SCT) was performed on 20 of the patients who responded to chemotherapy, 7 of whom were in at least partial remission at the time and 13 of whom had SCT done as salvage therapy for relapsed or refractory RT. Cumulative 3-year-survival was 75% in those who underwent SCT after remission compared to 21% of patients who underwent SCT for relapsed/refractory RT. These data suggest that SCT is a promising treatment option for patients with RT if they can achieve remission with chemotherapy. It also highlights the need for new therapies to induce remission in this aggressive disease.

Clinical Course

On initial presentation, the patient in question had many of the clinical features what were associated with CLL transformation to RT: progressive lymphadenopathy, systemic symptoms (night sweats), an elevated LDH to 1109, and a history of at least 4 prior treatments. SPEP showed no monoclonal gammopathy, but this may have been due to his underlying hypogammaglobulinemia. His PET-CT showed an elevated SUV of 13.4 in his cervical lymph nodes. His RT score of 4 on admission portended a very poor prognosis.

Given this patient's limited life expectancy, he was offered the choice of treatment with chemotherapy or supportive care. He elected to return home with hospice. The Palliative care team provided therapies to control his cough, dyspnea, and improve his nutrition. He died at home two days after discharge.

Conclusion

This case highlights the rare transformation of CLL to RT and illustrates the rapid progression of disease in those with high-risk features. Given these factors, a Palliative Care consultation should be considered in all patients with newly diagnosed with RT to aid with symptom management and help patients establish and meet their goals of care.

REFERENCES

1. **Rossi D, Cerri M, Capello D, Deambrogi C, Rossi FM, Zucchetto A, De Paoli L, Cresta S, Rasi S, Spina V, Franceschetti S, Lunghi M, Vendramin C, Bomben R, Ramponi A, Monga G, Conconi A, Magnani C, Gattei V, Gaidano G**. Biological and clinical risk factors of chronic lymphocytic leukaemia transformation to Richter syndrome. *Br J Haematol*. 2008 Jun;142(2):202-15. doi:10.1111/j.1365-2141.2008.07166.x. Epub 2008 May 19. PubMed PMID: 18492108.
2. **Robertson LE, Pugh W, O'Brien S, Kantarjian H, Hirsch-Ginsberg C, Cork A, McLaughlin P, Cabanillas F, Keating MJ.** Richter's syndrome: a report on 39 patients. *J Clin Oncol*. 1993 Oct;11(10):1985-9. PubMed PMID: 8410123.
3. **Tsimberidou AM, Keating MJ**. Richter syndrome: biology, incidence, and therapeutic strategies. *Cancer*. 2005 Jan 15;103(2):216-28. Review. PubMed PMID:15578683.
4. **Tsimberidou AM, O'Brien S, Khouri I, Giles FJ, Kantarjian HM, Champlin R, Wen S, Do KA, Smith SC, Lerner S, Freireich EJ, Keating MJ**. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. *J Clin Oncol*. 2006 May 20;24(15):2343-51. PubMed PMID: 16710033.

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