



## Second Malignancies in Chronic Lymphocytic Leukemia

Erin Streu, RN, MN, CON(C)

A 73-year-old patient named Mr. G was diagnosed with Rai stage 0 chronic lymphocytic leukemia (CLL) in 2007. The diagnosis was made incidentally by a routine complete blood count that reported lymphocytosis, and the diagnosis was confirmed by flow cytometry. His family history for cancer only included a sister previously diagnosed with melanoma. Because of his early stage, he was followed in clinic and remained asymptomatic for three years. He then presented with supraclavicular and bilateral axillary lymphadenopathy measuring 4–6 cm, a rising white blood cell count of 43,620 u/L, and hemoglobin and platelet count slightly less than normal (12 g/dl and 136,000 u/L, respectively). Mr. G was started on chlorambucil and, after two months of treatment, was held because of a generalized papular erythematous rash covering 40% of his back, chest, and arms. He was referred to dermatology for assessment, and biopsy confirmed the rash as leukemic infiltration of the skin. A second biopsy performed on a 2 cm lesion found incidentally behind his right ear was positive for basal cell carcinoma (BCC).

Mr. G's chemotherapy was switched to a more aggressive regimen of fludarabine and rituximab (FR) that he tolerated for a full six cycles. During this time, Mr. G developed a 1.5 x 1 cm ulcerated lesion on his right external ear, near the helix, requiring reconstruction (see Figure 1). This was performed after the completion of chemotherapy. Mr. G had a wide wedge excision with double flap closure for a moderately differentiated infiltrating squamous cell carcinoma (SCC) extending to cartilage surface. Six months later, he developed T4a, N1 recurrent SCC requiring subtotal auriclectomy including lateral temporal bone resection, parotidectomy, and neck

dissection followed by adjuvant radiotherapy 50 Gy in 20 fractions.

One year later, Mr. G's CLL relapsed with multiple sites of lymphadenopathy, thrombocytopenia, a palpable abdominal mass, and maculopapular lesions appearing to be consistent with his previous cutaneous involvement. Also noted was a 3 cm lesion to the left cheek that grew rapidly and, in three months, was later biopsied and diagnosed as moderately differentiated SCC (see Figure 2). Mr. G went on to be treated with radiotherapy. Chemotherapy (FR regimen) was once again initiated for his CLL and, after two cycles of treatment, his white blood cell count was responding, but he reported a 30-pound weight loss, drenching night sweats, and lactate dehydrogenase 10 times the upper limits of normal with palpable preauricular, cervical, supraclavicular adenopathy, and bulky axillary nodes measuring greater than 5 cm. A computed tomography scan of his abdomen found a large abdominal mass measuring 32 cm x 15 cm. Mr. G was referred to surgical oncology for biopsy to rule out a Richter transformation to a more aggressive lymphoma.

### Pathophysiology

CLL is the most commonly diagnosed adult leukemia, characterized by proliferation of B-cell lymphocytes, lymphadenopathy, and splenomegaly, as well as progressive defects in both cell-mediated and humoral immunity. Although generally considered an indolent condition, the disease course for CLL remains highly variable, from watchful waiting to multiple chemotherapeutic regimens that result in chronic immunosuppression and impaired resistance to infectious complications (Moran, Browning, & Buckby, 2007). Common

causes of death for patients diagnosed with CLL include progressive disease, infectious complications, and secondary malignancies (Beiggi, Lambert, Pitz, Sefitel, & Johnston, 2012; Wierda et al., 2009; Yoon et al., 2012). A Canadian population study examining 612 patients from 1998–2003 found 24% of patients with CLL to have a prior history of cancer at the time of their diagnosis, and of the remaining 455 cases that were followed for a median of 6.4 years, 23% developed a second malignancy (Beiggi et al., 2012).

Researchers have widely recognized that the risk of developing a second cancer is higher in patients living with CLL than the general public; however, the exact mechanism of action is unknown (Royle, Baade, Joske, Girshik, & Fritschi, 2011; Wiernik, 2004). The underlying abnormality in immune function related to the disease itself may partly explain the increased incidence of secondary cancers, and often patients have multiple immune cell defects affecting B and T cells, natural killer cells, and dendritic cells that further heighten this risk by impairing the T-cell response to tumor cells (Molica, 2005). Standard chemotherapeutic treatments include the use of purine analogs such as fludarabine and alkylating agents such as cyclophosphamide that can induce complete and potentially long-lasting remissions but are associated with prolonged immunosuppression and suppressed immune surveillance (Wadhwa & Morrison, 2006). Immune system impairment, such as slow recovery of lymphocytes, may disrupt the immune surveillance equilibrium of tumor control and escape (Barrett & Le Blanc, 2009). The inherent predisposition to malignancy coupled with the significant effects of chemotherapy may contribute to an overall higher risk of secondary malignancy. The presence of a detection bias in a population



**Figure 1. Healed Area Post-Auriclectomy and Radiotherapy**

Note. Image courtesy of CancerCare Manitoba. Used with permission.

of patients receiving routine and regular follow-up with a knowledgeable oncology specialist may explain higher incidence rates.

## Epidemiology and Risk Factors

The reporting of two and even three malignancies in patients with CLL is occurring with increasing frequency. Retrospective data show patients with CLL have a three-fold risk of developing a secondary malignancy, an 8–15 fold increased risk for developing skin cancers, and, when skin cancers are excluded, the overall risk is twice that of age- and gender-matched control populations (Beiggi et al., 2012; Tsimberidou et al., 2009). The risk appears to be constant for men and women, regardless of age or treatment history (Beiggi et al., 2012). Men seem to be at higher risk for nonmelanoma skin cancer (NMSC) and prostate cancer, whereas women are more likely to develop breast, lung, and gastrointestinal cancers (Beiggi et al., 2012; Wiernik, 2004). Commonly diagnosed secondary malignancies include NMSC, Kaposi sarcoma, malignant melanoma, lung cancer, gastrointestinal malignancies, breast cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancers, and Richter transformation to a very aggressive large B-cell lymphoma (Beiggi et al., 2012; Jain & O'Brien, 2012;

Molica, 2005; Royle et al., 2011; Wiernik, 2004).

Although all patients with CLL should be counseled regarding their increased risk for developing a second malignancy, independent factors have been identified that may be predictive of the development of other cancers. These include older age (older than age 60 years), male gender, and elevated levels of beta 2 microglobulin (greater than 3 mg/L), lactate dehydrogenase (greater than 618 u/L), and serum creatinine (greater than 1.6 mg/gL) (Tsimberidou et al., 2009). Risk reduction and health promotion strategies could be stratified based on these criteria to assist clinicians in targeting education and interventions for CLL populations.

Of particular concern is the increasing prevalence of skin cancers in patients diagnosed with CLL. BCC and SCC of the skin are being seen more frequently in the clinical setting (Beiggi et al., 2012). Precancerous precursor conditions, such as merkel cell tumors and Bowen disease, or SCC of the skin in-situ, also are becoming more frequently associated with patients with a CLL diagnosis (Wiernik, 2004). Specific incidence rates are not yet known, but small case studies suggest that SCC appears to be more predominant and occurs in 3%–10% of patients with CLL (Albregts et al., 1998; Robak & Robak, 2007).

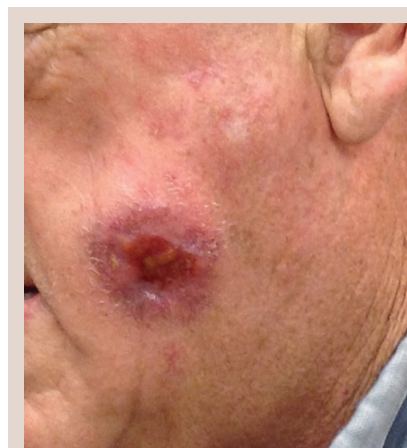
Although SCC usually tends to have a relatively slow growth pattern, it appears more aggressive in the setting of CLL and has a higher tendency for local recurrence and lymph node involvement than BCC. This makes management and intervention more complex and challenging (Albregts et al., 1998; Hartley, Searle, Breach, Rhys-Evans, & Henk, 1996; Levi, Randimbison, Te, & La Vecchia, 1996; Mehrany, Weenig, Pittelkow, Roenigk, & Otley, 2004; Wiernik, 2004). The atypical histology of BCC or SCC of the skin in patients with CLL also is associated with significantly higher rates of recurrence after standard treatment for skin cancer with Mohs surgery, potentially because of the increased incidence of regional lymph node metastasis and high-grade tumors (Dasanu & Alexandrescu, 2007). Frierson, Deutsch, and Levine (1988) reported a case series of 12 patients with CLL in which 32 cases of SCC lesions of the head and neck were found. Four of the 12 patients had evidence of metastatic disease and, of these 32 cases, 56% of the lesions were considered high grade. Characteristics

of suspicious skin lesions include the following.

- Any new pigmented lesion
- Changing pigmented lesion
- Persistent papule, nodule, or patch (pigmented or nonpigmented)
- Atypical features including rolled border, central crater, ulceration, or pain
- Any persistent papule, nodule, or plaque that does not resolve with treatment
- Characteristic features of a premalignant lesion (atypical mole, actinic keratosis, congenital nevus, or nevus sebaceous).

## Nursing Considerations and Implications for Nursing

At all stages of the disease trajectory, patients with CLL require hematologic monitoring and assessment for disease progression. In light of reports highlighting the increased risk for secondary cancers in this population, clinical assessment cannot focus solely on the disease state of CLL. Because of the chronic nature of the disease, patients require long-term monitoring for second malignancies, and nurses are in a unique position to provide this level of skilled and comprehensive care. Assessments and counseling should incorporate current cancer screening guidelines into practice. Nurses need to be able to identify and recognize early signs and symptoms of malignancy and be prepared to intervene immediately and appropriately. Skin self-examination is a simple and inexpensive screening method for skin



**Figure 2. Squamous Cell Carcinoma Lesion**

Note. Image courtesy of CancerCare Manitoba. Used with permission.

## Second Malignancies in Chronic Lymphocytic Leukemia

- Patients diagnosed with chronic lymphocytic leukemia (CLL) have a two-fold increased risk of developing a second malignancy, regardless of age, gender, or treatment history.
- Second malignancies in patients with CLL tend to be more aggressive, respond less favorably to treatment, and have a higher risk of mortality.
- The prevalence of nonmelanoma skin cancers (basal cell and squamous cell carcinoma) is rising in clinical practice, with lesions more likely to metastasize and/or recur.
- Clinical factors associated with an increased risk of malignancy include older age, male gender, and elevated beta 2 microglobulin, creatinine, and lactate dehydrogenase levels.
- Healthcare providers should encourage patients to adhere to age- and gender-specific screening practices such as colonoscopy, mammography, self-skin examination, and a healthy lifestyle, including smoking cessation, sun hygiene, and optimal body mass index.
- Nursing assessments should include questions regarding risk factors for malignancy, a family history of cancer, current tobacco and alcohol use, and an up-to-date list of screening practices undertaken by the patient and primary care physician.

- Education materials should highlight the increased risk of developing a second malignancy associated with a CLL diagnosis and the importance of early reporting of persistent or worrisome symptoms to healthcare providers.

### Bibliography

- Albregts, T., Orengo, I., Salasche, S., Duncan, L., Sillman, J., & Hassoun, H. (1998). Squamous cell carcinoma in a patient with chronic lymphocytic leukemia: An intraoperative diagnostic challenge for the Mohs surgeon. *Dermatologic Surgery*, 24, 269–272. doi:10.1111/J.1524-4725.1998.tb04141.x
- Beiggi, S., Lambert, P.J., Pitz, M., Seftel, M.D., & Johnston, J.B. (2012). Risk of second malignancies in patients with chronic lymphocytic leukemia: A population-based Canadian study [Abstract 5505]. *Cancer Research*, 72(8, Suppl. 1). Retrieved from <http://bit.ly/1crhZnL>
- Champion, V.L., & Rawl, S.M. (2005). Secondary prevention of cancer. *Seminars in Oncology Nursing*, 21, 252–259.
- Vargo, N. (2003). Basal cell and squamous cell carcinoma. *Seminars in Oncology Nursing*, 19, 12–21.

cancer that nurses can promote (Vargo, 2003). Additional assessment of suspicious or persistent lesions by a healthcare provider and referral to dermatology can minimize the negative impact and effects of skin cancer.

Cancer screening guidelines are well documented, evidence-based, and easily accessible regardless of geography, and can be encouraged and implemented in the clinical setting (American Cancer Society, 2013; American Society of Clinical Oncology, 2012; National Cancer Institute, n.d.). The responsibility, however, to adhere to these screening practices falls to the patient and, without proper counseling, patients may perceive them as unnecessary, unimportant, or inconvenient. Nurses must educate and inform patients not only of their increased risk but also of the potentially more aggressive nature of the malignancy (Champion & Rawl, 2005). Patients should be encouraged to engage in health-promoting behaviors such as cancer screening; risk-reduction strategies such as smoking cessation, skin protection, and sun hygiene practices (World Health Organization, 2013); healthy eating; and daily exercise. Communication with patients' other healthcare providers regarding the risk of secondary malignancies is essential so that early detection is facilitated.

Erin Streu, RN, MN, CON(C), is a clinical nurse specialist—lymphoma at Cancer

Care Manitoba in Winnipeg, Manitoba, Canada. No financial relationships to disclose. Streu can be reached at [erin.streu@cancercare.mb.ca](mailto:erin.streu@cancercare.mb.ca), with copy to editor at [ONFEditor@ons.org](mailto:ONFEditor@ons.org).

**Key words:** late effects, leukemia, lymphoma, hematology, ambulatory care, clinical practice

Digital Object Identifier: 10.1188/14.ONF.95-98

### References

- Albregts, T., Orengo, I., Salasche, S., Duncan, L., Sillman, J., & Hassoun, H. (1998). Squamous cell carcinoma in a patient with chronic lymphocytic leukemia: An intraoperative diagnostic challenge for the Mohs surgeon. *Dermatologic Surgery*, 24, 269–272. doi:10.1111/J.1524-4725.1998.tb04141.x
- American Cancer Society. (2013). American Cancer Society guidelines for the early detection of cancer. Retrieved from <http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer>
- American Society of Clinical Oncology. (2012). Cancer.Net: Cancer screening. Retrieved from <http://www.cancer.net/all-about-cancer/risk-factors-and-prevention/cancer-screening>
- Barrett, J., & Le Blanc, K. (2009). Cancer chemotherapy and immune regulation. *American Journal of Immunology*, 5, 8–16. doi:10.1172/JCI31405
- Beiggi, S., Lambert, P.J., Pitz, M., Seftel, M.D., & Johnston, J.B. (2012). Risk of second malignancies in patients with chronic lymphocytic leukemia: A population-based Canadian study [Abstract 5505]. *Cancer Research*, 72(8, Suppl. 1). Retrieved from <http://bit.ly/1crhZnL>
- Champion, V.L., & Rawl, S.M. (2005). Secondary prevention of cancer. *Seminars in Oncology Nursing*, 21, 252–259.
- Dasanu, C.A., & Alexandrescu, D.T. (2007). Risk for second nonlymphoid neoplasms in chronic lymphocytic leukemia. *Medscape General Medicine*, 9(4), 35–48.
- Frierson, H., Deutsch, B., & Levine, P. (1988). Clinicopathological features of cutaneous squamous cell carcinomas of the head and neck in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma. *Human Pathology*, 19, 1397–1402.
- Hartley, B., Searle, A., Breach, N., Rhys-Evans, P., & Henk, J. (1996). Aggressive cutaneous squamous cell carcinoma of the head and neck in patients with chronic lymphocytic leukaemia. *Journal of Laryngology and Otology*, 110, 694–695.
- Jain, P., & O'Brien, S. (2012). Richter's transformation in chronic lymphocytic leukemia. *Oncology*, 26, 1146–1152. doi:10.1186/1478-811X-10-43
- Levi, F., Randimbison, L., Te, V.C., & La Vecchia, C. (1996). Non-Hodgkin lymphomas, chronic lymphocytic leukemias, and skin cancers. *British Journal of Cancer*, 74, 1847–1850.
- Mehran, K., Weenig, R., Pittelkow, M., Roenigk, R., & Otley, C. (2004). High recurrence rates of basal cell carcinoma after Mohs surgery in patients with chronic lymphocytic leukemia. *Archives*



- of *Dermatological Research*, 140, 985–988. doi:10.1001/archderm.140.8.985
- Molica, S. (2005). Second neoplasms in chronic lymphocytic leukemia: Incidence and pathogenesis with emphasis on the role of different therapies. *Leukemia and Lymphoma*, 46, 49–54. doi:10.1080/10428190400007524
- Moran, M., Browning, M., & Buckby, E. (2007). Nursing guidelines for managing infections in patients with chronic lymphocytic leukemia. *Clinical Journal of Oncology Nursing*, 11, 914–924. doi:10.1188/07.CJON.914-924
- National Cancer Institute. (n.d.). Screening and testing to detect cancer. Retrieved from <http://www.cancer.gov/cancer-topics/screening>
- Robak, E., & Robak, T. (2007). Skin lesions in chronic lymphocytic leukemia. *Leukemia and Lymphoma*, 48, 855–865. doi:10.1016/j.jaad.2008.08.047
- Royle, J.A., Baade, P.D., Joske, D., Girshik, J., & Fritschi, L. (2011). Second cancer incidence and cancer mortality among chronic lymphocytic leukemia patients: A population-based study. *British Journal of Cancer*, 105, 1076–1081. doi:10.1038/bjc.2011.313
- Tsimberidou, A.M., Wen, S., McLaughlin, P., O'Brien, S., Wierda, W.G., Lerner, S., . . . Keating, M. (2009). Other malignancies in chronic lymphocytic leukemia/small lymphocytic lymphoma. *Journal of Clinical Oncology*, 27, 904–910. doi:10.1200/JCO.2008.17.5398
- Vargo, N. (2003). Basal cell and squamous cell carcinoma. *Seminars in Oncology Nursing*, 19, 12–21.
- Wadhwa, P.D., & Morrison, V.A. (2006). Infectious complications of chronic lymphocytic leukemia. *Seminars in Oncology Nursing*, 33, 240–249.
- Wierda, W.G., O'Brien, S., Wang, X., Faderl, S., Ferrajoli, A., Do, K.A., . . . Keating, M. (2009). Characteristics associated with important clinical end points in patients with chronic lymphocytic leukemia at initial treatment. *Journal of Clinical Oncology*, 27, 1637–1643. doi:10.1200/JCO.2008.18.1701
- Wiernik, P.H. (2004). Second neoplasms in patients with chronic lymphocytic leukemia. *Current Treatment Options in Oncology*, 5, 215–223.
- World Health Organization. (2013). Sun protection. Retrieved from [http://www.who.int/uv/sun\\_protection/en](http://www.who.int/uv/sun_protection/en)
- Yoon, J.Y., Lafarge, S., Dawe, D., Lakhi, S., Kumar, R., Morales, C., . . . Johnston, J.B. (2012). Association of interleukin-6 and interleukin-8 with poor prognosis in elderly patients with chronic lymphocytic leukemia. *Leukemia and Lymphoma*, 53, 1735–1742.

### Do You Have an Interesting Clinical Experience to Share?

Clinical Challenges provides readers with a forum to discuss creative clinical solutions to challenging patient care issues. Case studies or descriptions may be submitted with or without discus-

sion or solutions. Materials or inquiries should be directed to *Oncology Nursing Forum* Associate Editor Anne Marie C. Flaherty, MSN, RN, APNc, at [aflaherty@HackensackUMC.org](mailto:aflaherty@HackensackUMC.org).