

## **Second Malignancies in Chronic Lymphocytic Leukemia**

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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, Seftel, & 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, & Fritischi, 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