Skin Cancer in Patients With Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

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Abstract: The association between non-Hodgkin lymphoma, including chronic lymphocytic leukemia, and aggressive skin cancers is well established. This review highlights existing data that address increased incidence and clinical characteristics of skin cancers in patients with non-Hodgkin lymphoma—specifically, chronic lymphocytic leukemia. Patients with non-Hodgkin lymphoma have worse outcomes when melanoma and nonmelanoma skin cancers develop. The poorer outcomes in these patients are evidenced by increased rates of local recurrence, regional metastasis, and death. Lymphoproliferative neoplasms and certain skin cancers may share similar pathogenic factors, which could provide insights regarding their close relationship and the behavior of lymphoma-related skin cancers. As a consequence of the poorer prognosis in patients with lymphoma-related skin cancer, more aggressive therapeutic measures could reduce the risk of skin cancer recurrence, metastasis, and death. Strategies such as sun protection, education, and frequent dermatologic examinations may help prevent and successfully treat skin cancers in patients with lymphoma.

Keywords
Chronic lymphocytic leukemia, melanoma, non-Hodgkin lymphoma, skin neoplasms

Introduction

Non-Hodgkin lymphoma (NHL) encompasses a diverse group of lymphoproliferative cancers. It is more common in developed regions, such as North America; Australia; New Zealand; and Northern, Western, and Southern Europe.[1] NHL is the seventh most common cancer in the United States.[2] Chronic lymphocytic leukemia (CLL) is a member of the NHL family. It is a low-grade lymphoproliferative malignancy characterized by clonal proliferation of B cells, and it represents 25% of all leukemias in developed countries.[3]

A number of reports describe the increased risk of many forms of cancers in patients with NHL. Such cancers include brain cancer, malignant melanoma (MM), lung carcinoma, nonmelanoma skin cancers (NMSCs), Hodgkin disease,[4-7] Kaposi sarcoma, Merkel cell carcinoma (MCC), eruptive multiple piloleiomyomas, mycosis fungoides, and metastatic adnexal tumors, such as atypical fibrox-

anthoma and microcystic adnexal carcinoma.[8-13] Many studies describe the increased incidence and aggressiveness of skin cancer in patients with lymphoma. Interestingly, a number of reports also describe an inverse association whereby patients with MM or NMSC are at increased risk for NHL.[14] The diagnosis of skin cancer is common, and therefore it is imperative to obtain high-quality research to validate the association between skin cancer and NHL. This article will review the data on the epidemiology, clinical characteristics, pathogenesis, prevention, and treatment of skin cancer in the clinical setting of NHL.

Epidemiologic Factors

A few studies have demonstrated increased risk of NMSC and MM in patients with NHL. The highest-quality data come from large, population-based studies conducted in Denmark, Sweden, and Switzerland.[3,4,6,14,15] One such study, from Switzerland, showed that patients with CLL had increased risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC; standardized incidence ratio, 5.0 and 2.7, respectively).[14] A study conducted in the United States reported that patients with CLL were 8 times more likely to have skin cancer than patients without CLL.[15] In addition to SCC, BCC, and MM, other rare skin cancers—such as Kaposi sarcoma, eruptive multiple piloleiomyomas, mycosis fungoides, metastatic atypical fibroxanthoma, metastatic microcystic adnexal carcinoma, and MCC—have been reported in patients who have NHL.[5,8-13]

In the studies describing an inverse association whereby patients with MM or NMSC are at increased risk for NHL, this risk varied from 1.1–2.6 times higher than average.[14] Moreover, NHL patients who had a prior diagnosis of skin cancer have a higher mortality rate from NHL.[16,17] This increased mortality rate is not thought to be due to death from skin cancer metastasis. These findings suggest that patients who present with NHL and a prior diagnosis of skin cancer should be considered for thorough surveillance and, potentially, for more aggressive therapy. In addition to an increased incidence of skin cancer, patients with NHL are also at increased risk for more aggressive forms of skin cancer, as evidenced by higher rates of recurrence, regional metastasis, and death.[18-22]

A study of patients with BCC treated with Mohs micrographic surgery found a 5-year recurrence rate of 22% in patients with a prior diagnosis of CLL.[18] This reported recurrence rate of BCC in the clinical setting of CLL was 14 times higher than for control subjects without CLL, even when the patients had similar preoperative tumor sizes and histologic subtypes. As with BCC, SCC treated with Mohs micrographic surgery was also reported to have an increased recurrence rate in patients with CLL. A 5-year recurrence rate of 19%—a rate 7 times higher than in control subjects—was reported in these patients with SCC who had a prior diagnosis of CLL.[19]

Patients with CLL who have skin cancer also have higher rates of metastasis and death. Investigators in Australia demonstrated that patients with CLL had increased risk of death due to MM and NMSC (standardized mortality ratios [SMRs], 4.79 and 17.0, respectively).[21] Another study of patients with CLL who developed SCC showed a 5-year metastatic rate of 18% and an eventual mortality rate of 11%; the metastatic rates were the same for patients with CLL treated with chemotherapy and patients with CLL treated with observation alone.[20] In this study, all metastases initially involved the regional lymph nodes. Hence, patients who have CLL and SCC with aggressive clinical or histopathologic features should be considered for sentinel lymph node biopsy.

Some population-based studies have shown that MM occurs 2.3–3.1 times more often in patients with CLL.[5,23] Although data on the outcomes of MM are limited, patients with CLL in whom MM develops have been reported to have poorer outcomes. A recent Surveillance Epidemiology and End Results population-based study demonstrated decreased overall survival in patients with MM and a history of CLL (SMR, 2.6). MM cause-specific survival was also worse in these patients, with a reported SMR of 2.8.[22] This same study also reported poor outcomes for patients with MCC and a prior diagnosis of CLL; overall survival and MCC cause-specific survival were worse in the clinical setting of CLL, with reported SMRs of 3.1 and 3.8, respectively.[22] As a result of the poorer outcomes in patients who have MM, MCC, and NMSC in the clinical setting of NHL, a more aggressive approach should be considered in the treatment of these skin cancers in patients with NHL.

Mechanism and Pathogenesis of the Increased Incidence of Skin Cancers in NHL

Several pathogenic factors are thought to be involved in the increased association of skin cancer and NHL. Some investigators have proposed that the immunosuppressive effects of chemotherapeutic agents have a role in the association.[24] In addition, ultraviolet (UV) radiation may also be involved in the development of NHL.[25] Well-established data support the association between UV radiation and skin cancer[26]; however, the evidence regarding the role of UV radiation in NHL is inconclusive.[25] Impaired functioning of the immune system is also thought to play a considerable role in the development and clinical characteristics of MM, NMSC, and NHL.[27] Sunlight can cause immunosuppression,[28] and one study found a correlation between sunlight and the incidence of NHL and MM (but not CLL).[25]

Immunosuppression has served as the basis for many hypotheses on the association between NHL and skin cancer. In NHL, immunosuppression occurs amid impaired immune surveillance and the cytotoxic function of lymphocytes. In a healthy person, the immune system prevents the development of such immune-responsive tumors as MM and NMSC by suppressing and eliminating mutagenic events that would otherwise progress to full cancers. This concept of immunosuppression-related skin cancer is similar to the increased incidence of skin cancer in recipients of an organ transplant.[29] In NHL, the dysfunctional B cells may also have an important part in immunosuppression.[30] Proliferation of dysfunctional, malignant cells leads to a decreased amount of normal cells. Investigators have demonstrated that leukemic B cells secrete immunosuppressive factors and also downregulate the expression of CD40 ligand (CD154) on activated T cells.[31] The combined effect of increased immunosuppressive factors and decreased expression of CD154 impairs the interaction of activated T cells with normal B cells and other antigen-presenting cells.[31] CD154 is also involved in T-cell–dependent immunoglobulin class switching, and its downregulation may result in low levels of certain immunoglobulin G subclasses.[32]

Other mechanisms for immunosuppression in patients with NHL include low complement levels, altered leukemic cell expression of major histocompatibility complex antigen, hypogammaglobulinemia, impaired granulocyte and bystander T-cell function, and altered T-cell–receptor variable regional gene expression.[33] Many reports suggest that in CLL, the dysfunctional lymphocytes are unable to elicit an antitumor response, thereby contributing to the increased incidence and clinical characteristics of BCC, SCC, MM, and other forms of skin cancers in these patients.[18-20,23]

Existing data also suggest that the immunosuppressive effects of chemotherapeutic agents and irradiation used to treat NHL increase the risk of skin cancer in these patients.[24] Yet, some investigators argue that the increased susceptibility to secondary cancers is solely due to the leukemic process—rather than the effects of treatment—because the risk persists long after the treatment period.[15] Nevertheless, the chemotherapeutic agents used in NHL have severe immunosuppressive effects and may well have an additional role in the development and aggressiveness of skin cancers. Alkylating agents, such as chlorambucil (Leukeran, GlaxoSmithKline) and cyclophosphamide, have been associated with increased risk of acute myeloid leukemia, and nucleoside analogues, such as fludarabine (Fludara, Sanofi-Aventis), have been associated with secondary cancers, including skin cancer.[24] The fact that these types of chemotherapy are frequently used in patients with NHL causes speculation about the true role of chemotherapy in lymphoma-associated skin cancer.

Other postulates for the association of skin cancer and NHL are inconclusive. These postulates include genetic abnormalities, including aberrations due to viral pathogens, HLA-associated variation, and environmental insults.[34]

Genetics

A shared genetic abnormality could be the cause of the association between NHL and skin cancer. Some common genetic aberrations are seen in patients with lymphoma and those with skin cancer. The tumor suppressor gene *p53* is located on the short arm of chromosome 17 and is commonly mutated in cancers affecting humans. It has been linked to lymphomas and skin cancers. In fact, 50% of sporadic BCCs have a *p53* mutation.[35,36] This mutation is also found in 41–69% of SCCs[26,35] and has been associated with MM as well. In CLL, deletion in the short arm of chromosome 17 occurs 7–10% of the time and is the strongest predictor of poor prognosis in these patients.[37] Another commonly mutated gene in CLL is *BCL-2*. This gene suppresses programmed cell death, which aids in prolonging cell survival. Patients with CLL have high levels of *BCL-2*[38]; patients with MM also have an elevated level of *BCL-2*.[39] In conjunction with mutations in *p53*, these findings may be influential in the increased risk and more aggressive features seen in skin cancers in these patients.

Challenges With the Histologic Diagnosis of Skin Cancer in NHL

The assessment of a histologic specimen of skin cancer in patients with NHL is usually complicated by the presence of a dense peritumoral lymphocytic infiltrate.[40] Moreover, the presence of a peritumoral infiltrate can obscure the extension of the tumor, thereby making margin assessment and diagnosis more challenging. Some investigators speculate that the aggressive behavior of NMSC in patients with CLL may be due to the presence of peritumoral infiltrates of dysfunctional lymphocytes.[18,19]

The composition of peritumoral infiltrates has been analyzed in previous reports, showing that these infiltrates, observed in 36% of cases, were composed of B-cell leukemic cells 75% of the time.[41] These dysfunctional CLL B cells are unable to suppress tumor growth and could increase the chances of subclinical tumor extension with more aggressive features and larger surgical defects.[18,19] In addition, a dense peritumoral infiltrate may obscure the margins of excision specimens and that of Mohs micrographic surgery. Immunostains may be beneficial in these situations to help view residual NMSC by highlighting tumor cells at the margin surrounded by dense lymphocytic infiltrates.[40,42]

Numerous hypotheses have been presented to explain the high recurrence rates of skin cancer in CLL. One hypothesis is the possibility of a new tumor colliding with

a scar at the site where the primary cancer was treated. Although patients with NHL have higher incidences of skin cancer, this clinical scenario is less likely than increased recurrence of the primary tumor. In addition, the dampened and inadequate immunologic response in patients with CLL may cause incomplete and patchy tumor regression, resulting in discontiguity of the tumor. This inadequate immunologic response could increase the risk of intradermal metastases that are not completely cleared by Mohs micrographic surgery. Finally, immunosuppression caused by chemotherapeutic agents used to treat NHL may increase recurrence rates and aggressiveness of skin cancer in these patients.[24]

Treatment of Skin Cancer in Patients With NHL

Patients with NHL who develop skin cancer also have poorer outcomes, as evidenced by higher rates of local recurrence, regional metastasis, and death than patients without NHL. As a result of these poorer outcomes, more aggressive treatment approaches could be considered.

Meticulous control of histologic margins with Mohs micrographic surgery is important for patients with CLL and NMSC. Mohs micrographic surgery provides a high cure rate and therapeutic advantage in NMSC; however, the procedure may not have the expected success rate in lymphoma. As a result of the inadequate immunologic response that occurs in CLL, patients with NMSC may have discontiguous tumors. Given the high recurrence rates of NMSC in CLL patients, it may be beneficial to remove additional margins of tissue for histologic examination with immunostains. The benefit of this additional measure has not been proven, but it is thought that resection of additional tissue ensures complete removal of the tumor, especially given a high possibility of discontiguous spread.

Another method that could be used for management of discontiguous tumors involves postoperative adjuvant radiation therapy to the tumor bed and surrounding skin.[43] This approach may be beneficial in the treatment of NMSC with aggressive clinical and histopathologic attributes—such as perineural invasion, poor differentiation, large tumor diameter, and increased tumor depth—in patients with NHL.

Unfortunately, resection of additional tissue and adjuvant radiation therapy may not be adequate in cases where metastasis has already occurred and the tumor has spread to regional lymph nodes. Reports that demonstrated an increased risk of metastasis and death in patients with CLL and SCC have also shown that the metastasis originally occurred in local lymph nodes.[20] Thus, it is important to properly assess lymph nodes in patients with lymphoma-associated skin cancer, especially in the clinical setting of CLL and SCC. Evaluation of lymph nodes could be carried out through sentinel lymph node biopsy. Palpation and imaging studies may also help in the early detection of nodal involvement. Characteristics of SCC that may favor sentinel lymph node biopsy include perineural invasion, a diameter greater than 2 cm, a depth greater than 6 mm, and poor differentiation.[44]

Apart from surgery and adjuvant radiation therapy, topical agents may be considered in the treatment of high-risk SCC. In a small study of 5 patients with CLL who had head and neck SCC in situ, the off-label use of imiquimod 5% cream 3 times weekly in conjunction with the cyclooxygenase inhibitor sulindac given at a dosage of 200 mg twice daily for 16 weeks resulted in clinical resolution and histologic clearing of the tumors in all patients.[45]

Prevention of Skin Cancer in Patients With NHL

Prevention strategies should be implemented early in patients with NHL to prevent NMSC development. Because excessive UV exposure has carcinogenic and immunosuppressive effects,[26,28] sun-protective measures are extremely important in patients with CLL, especially those who have other risk factors for skin cancers. Protection from the harmful effects of the sun can be achieved by applying a sunscreen with a sun protection factor of no less than 30 every day, wearing sun-protective clothing, seeking the shade, and avoiding outdoor activities during the peak daylight hours between noon and 2 PM. While employing strict sun-protective measures, patients with NHL may benefit from vitamin D supplementation to prevent deficiency.

To ensure early detection of NMSC, patients with NHL should be advised to carry out monthly self–skin checks at home. Yearly skin examination by a dermatologist to detect early forms of NMSC that are easily treated is also recommended. Any new, changing, or bleeding skin lesions should be examined thoroughly for any signs of malignancy and with a low threshold for biopsy. Dermatologists should also evaluate lymph nodes through palpation.

Patients with sun-damaged areas of the skin, actinic keratoses, or a prior history of skin cancer may benefit from chemopreventive measures, such as photodynamic therapy, topical chemotherapeutic regimens, or systemic retinoids.[46] Only retinoids have been shown to have true chemopreventive effects against NMSC, even though they are yet to be approved by the US Food and Drug Administration for use in patients with lymphoma.[47] Patients with a history of multiple and aggressive NMSCs may benefit from systemic retinoids[46]; isotretinoin is preferred in women of childbearing age.[48] Other chemopreventive agents shown to have promising results include topical 5-fluorouracil and imiquimod cream.[49]

Dietary changes and low-fat diets have been shown to decrease the risk of NMSC.[50] Animal studies have shown that high lipid levels exacerbate the mutagenic effects of UV radiation.[50]

Conclusion, Future Directions, and Research

Patients with NHL are at increased risk of more aggressive forms of skin cancer associated with poorer outcomes. Unfortunately, the incidence of both NHL and skin cancer is increasing, which poses problems for health care providers when treating these patients. Early detection and prompt aggressive treatment may reduce the risk of recurrence and metastasis of skin cancers in patients with CLL. Moreover, education of CLL patients about sun protection and early detection of cancer could reduce the rates of morbidity and death caused by skin cancer. Frequent follow-up with a low threshold for biopsy of new or growing lesions and aggressive treatment of precancerous and sun-damaged skin could also affect the outcomes in this special group of patients.

Innovation and research are needed to further elucidate the clinical characteristics and pathogenesis of skin cancer in patients with NHL/CLL. Research efforts should be directed at educational strategies, effective chemopreventive measures, genetics, optimal treatment, and the benefits of adjuvant therapy to markedly improve health outcomes in this patient population.

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