CASE IN POINT

SQUAMOUS CELL CARCINOMA OF THE ANUS IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA

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Many studies suggest a link between this type of leukemia and the development of additional primary malignancies, but an association with anal cancer has been largely overlooked.

The idea that patients with leukemia may be predisposed to developing additional primary malignancies was first suggested in 1878, when Whipman reported a case of pancreatic cancer in a patient with underlying leukemia.[1] Since then, numerous publications have supported the association between leukemia and other malignancies, particularly in patients with chronic lymphocytic leukemia (CLL).

Although the pathogenetic mechanism for this link is not completely understood, it's believed that immunosuppression inherent in CLL may play a key role. Here, we present the first detailed case report of a patient with CLL who developed squamous cell carcinoma of the anus. This case suggests that the risk of anal cancer, as with other types of malignancies, may be increased in patients with CLL and further implicates abnormal immune function as the probable cause of the propensity toward additional malignancies associated with a CLL diagnosis.

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INITIAL EXAM

A 77-year-old man presented to the Dallas VA Medical Center, Dallas, TX reporting rectal pain during defecation and streaks of bright red blood on the stool. These symptoms had occurred intermittently for three years and had become constant over the past two months. His medical history was notable only for low risk, Rai stage 0 CLL that had been found incidentally at another hospital seven years earlier and had never required treatment.

On physical examination, the patient had no palpable lymphadenopathy and no evidence of liver or spleen enlargement. Digital rectal examination revealed a firm mass along the left wall of the anal canal approximately 3 to 4 cm from the anal verge. A complete blood count revealed an elevated white blood cell count of 76 x 10^3/µL (normal, 4 to 11 x 10^3/µL), a low hemoglobin level of 10.6 g/dL (normal, 13 to 17.3 g/dL), and a normal platelet count of 2.3 x 10^5/µL. A white blood cell differential showed 99% lymphocytes and 1% neutrophils

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(normal, 37% to 80% neutrophils and 20% to 45% lymphocytes).

Peripheral blood immunophenotyping demonstrated a distinct population of lymphocytes comprising approximately 95% of the sample cells. Consistent with a diagnosis of B cell CLL, these cells expressed CD5, CD19, CD20, and CD23 glycoproteins and failed to express CD10.

Colonoscopy confirmed the presence of a 3-cm fungating mass along the left wall of the anal canal. Biopsies revealed squamous cell carcinoma. A computed tomography scan of the abdomen and pelvis showed no pathologically enlarged lymphadenopathy or other evidence of metastatic disease.

TREATMENT COURSE

The patient's anal mass was treated with concurrent chemotherapy (cisplatin and 5-flurouracil) and radiation therapy, which resulted in a complete tumor response. Three months after the completion of therapy, he remained disease free.

ABOUT THE CONDITION

CLL—which is characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen—is the most frequently diagnosed leukemia in Western countries. Classically, it is diagnosed in patients in their sixties and has a male predominance. Due to the increased frequency of blood count orders in recent years, approximately 60% of CLL diagnoses today are made when patients are asymptomatic. Prognosis for patients diagnosed with CLL is variable, with some having a normal life span, while others die within five years of diagnosis.[2]

Given that CLL is relatively common and typically affects elders, it might seem reasonable to dismiss an association between CLL and additional primary cancers as coincidental. Yet convincing epidemiologic data link CLL with subsequent malignancies. Two large reviews of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database found an elevated risk of second cancers—specifically, lung cancer, malignant melanoma, brain tumors, soft tissue sarcomas, and Hodgkin's disease—in patients with CLL.[3,4] In addition, a number of reports suggest that squamous cell carcinoma of the skin, which is not included in the SEER database, also occurs more frequently when CLL is present.[4–10] Case reports of gastric cancer,[11] Merkel cell tumor,[12] adenocarcinoma of the esophagus,[13] and small-cell carcinoma of the colon[14] also have been published.

Ours is the first detailed case report of a patient with CLL who developed squamous cell carcinoma of the anus. Two earlier series, published in 1965 and 1987, each reported on a patient with CLL and anal cancer but did not provide specifics of the cases (including histology).[7,10] Anal carcinoma is quite uncommon, representing only 0.003% of all cancer diagnoses.[15] Given this extremely low incidence, it's not surprising that the SEER reviews did not detect an increased risk of anal cancer in patients with CLL.

What's behind this increased risk of malignant disease in patients with CLL? Several hypotheses have been proposed. First, it's been suggested that ascertainment bias, as a result of the medical attention that comes with CLL diagnosis, could result in an increased detection of additional malignancies. If this were the case, however, one would expect that most of the second malignancies would be discovered around the time of CLL diagnosis. Yet both SEER reviews found that the heightened cancer risk was constant across all time intervals after CLL was diagnosed,[3,4] suggesting that ascertainment bias is not a significant contributor to this phenomenon.

A second possibility is that a common genetic or environmental factor predisposes patients to both CLL and the additional malignancy. After review of the SEER data on neoplasms associated with CLL, however, Greene and colleagues found no elevated risk of any type of leukemia following the diagnosis of these tumors.[3] The association, therefore, appears to be one-way, which argues against a common etiology for both tumors. Greene and colleagues also point out that their finding suggests that a CLL-associated "susceptibility state" may result in the development of additional primary malignancies.

The susceptibility state that has been implicated most often for the increased risk of second cancers associated with CLL is abnormal immune function. It's possible that drugs used to treat CLL might play a role in this, but the data at present are uncertain. In a 1990 report, the French Cooperative Group on Chronic Lymphocytic Leukemia demonstrated a higher incidence of epithelial cancer among patients with early stage, low risk CLL who were randomly assigned to receive indefinite treatment with chlorambucil 0.1 mg/kg/day (33 of 303 patients, or 11%) than among those who were randomly assigned to receive no treatment (19 of 309

patients, or 6%).[16] The authors, however, did not define the statistical significance of this finding.

Anecdotally, neither our patient nor many of those with second malignancies reported in other small series ever had received treatment for their CLL. Furthermore, neither of the two large SEER reviews demonstrated a clear association between CLL treatment and the risk of a second malignancy.[3,4] But virtually all of the data for these reviews were accumulated before the nucleoside analogues were commonly employed in CLL, and these drugs are well known to possess immunosuppressive effects. In fact, a case report published in 1997 showed remarkable progression of squamous cell carcinoma of the scalp following the institution of fludarabine in a patient with longstanding CLL.[17] Nevertheless, until more definitive data become available, we cannot assume that CLL treatment plays more than a modest role in the increased risk of second cancers.

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The immunosuppression of CLL itself has been well described. The disease is characterized by impaired B and T cell function, with resultant hypogammaglobulinemia and reduced spontaneous and antibody-dependent cellular cytotoxicity.[18] The clinical course of CLL frequently is complicated by recurrent bacterial and atypical infections and autoimmune phenomena.[2]

Furthermore, the pattern of second primary cancers observed in CLL is similar to that seen in patients receiving chronic immunosuppressive therapy following renal transplantation. Specifically, the frequencies of lung cancer, malignant melanoma, and squamous cell carcinoma of the skin are increased in both populations.[19,20] In addition, it has been observed that squamous cell carcinomas of the skin far outnumber basal cell carcinomas in patients with CLL and in those who've undergone renal transplantation—but not in immunocompetent patients.[10] These observations provide at least suggestive evidence that a similar perturbation in immune function is responsible for the increased incidence of second cancers seen in both of these patient groups.

It's interesting to note that chronic immunosuppression is a known risk factor for the development of squamous cell carcinoma of the anus.[21] Patients receiving immunosuppression following renal transplantation have a significantly increased incidence of squamous cell carcinomas of the anogenital region.[22,23] The risk is especially high in those with persistent human papillomavirus infection.[23]

It's at least plausible that similar immunologic incompetence, as a consequence of CLL, led to the development of anal cancer in our patient. One fact that argues against our supposition, is the lack of a clear link between CLL and cervical cancer, which has a similar pathogenesis to anal cancer.[3,4] Even so, it seems reasonable, overall, to conclude that patients with CLL may be at increased risk for anal cancer. ●

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