Diagnosis of chronic lymphocytic leukemia during Mohs micrographic surgery

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INTRODUCTION

B-cell chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the United States.[1] Patients are often asymptomatic but can present with leukemic infiltrates in the skin.[2] Here we report the case of a patient diagnosed with CLL during Mohs micrographic surgery (MMS) after leukemic infiltrates were noted on Mohs frozen sections.

Abbreviations used:

CD:	cluster of differentiation
CLL:	chronic lymphocytic leukemia
ECOG:	Eastern Cooperative Oncology Group
MMS:	Mohs micrographic surgery
SCC:	squamous cell carcinoma

CASE REPORT

A 74-year-old male with a history of atrial fibrillation, diabetes mellitus, and hypertension presented for MMS of a 2.0 cm, well differentiated squamous cell carcinoma (SCC) of the left forearm. During the first Mohs stage, a dense, monomorphic lymphocytic aggregate was noted in the dermis and subcutaneous fat (Fig 1, *A* and *B*). The tumor was cleared with MMS following 2 stages with standard hematoxylin and eosin frozen staining. This was followed by cytokeratin 5 immunohistochemistry on frozen en face sectioning to further analyze the dense inflammation for possible single-cell SCC infiltrates. Due to the presence of dense lymphocytic infiltrates, a complete blood count was ordered which revealed a lymphocyte predominant leukocytosis of 27.7 × 1000/mcL, concerning for a lymphoproliferative disorder such as CLL or the leukemic phase of a marginal zone lymphoma. The patient underwent further workup with peripheral blood flow cytometry and computed tomography of the chest, abdomen, and pelvis which showed mild splenomegaly, supporting the diagnosis of CLL. He also underwent FISH (Fluorescence in situ hybridization) panel testing for the detection of chromosomal aberrations commonly seen in CLL, which revealed trisomy 12 in 51% of cells. He is currently in surveillance given his good performance status with an ECOG (Eastern Cooperative Oncology Group) score of 0, with consideration for future treatment if significant disease related symptoms develop.

DISCUSSION

CLL is a hematologic neoplasm characterized by the production of immature monoclonal B lymphocytes.[1] Histology of cutaneous leukemic infiltrates in CLL shows nodular or diffuse aggregates of mature round lymphocytes that are typically positive for CD20 (cluster of differentiation 20), CD5, CD23, CD43.[3] The pathophysiology of leukemic infiltration in areas of primary cutaneous malignancies, such as SCC, remains unclear but may be a response of neoplastic leukocytes to tumor antigens, or due to tumor associated neovascularization.[4]

Recognition of atypical lymphocytic aggregates on frozen sections can aid in the diagnosis of CLL. In a study of 55 patients with CLL who underwent MMS,

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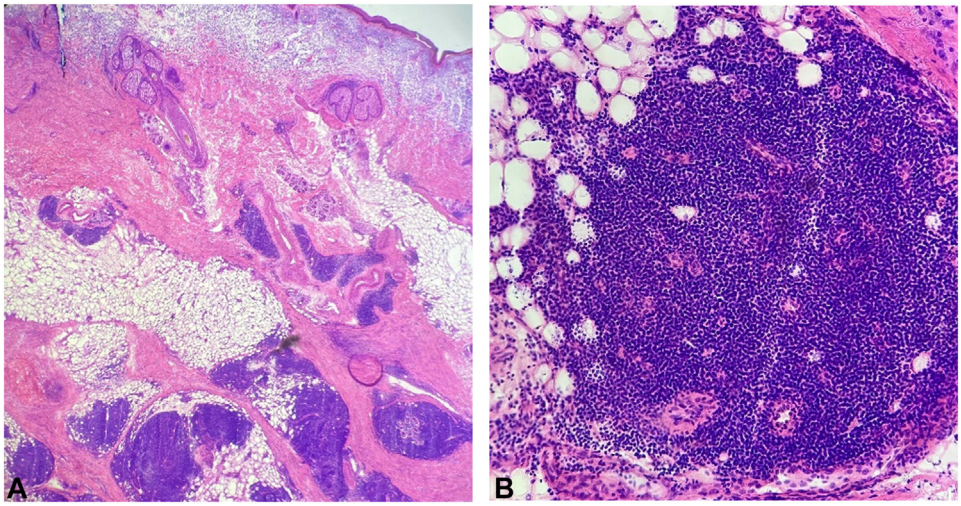

Fig 1. **A** and **B,** A dense, monomorphic lymphocytic infiltrate was noted in the dermis during the first stage of Mohs micrographic surgery of a 2.0 cm squamous cell carcinoma.

36% (20/55) of patients were noted to have leukemic infiltrates on frozen sections.[5] Padgett et al report the case of an otherwise asymptomatic patient who was diagnosed with CLL after lymphocytic infiltrates were identified on Mohs frozen sections.[4] Likewise, Maxfield et al report 3 cases of patients with atypical lymphocytic aggregates seen on frozen sections during MMS. Two of the patients had known diagnoses of CLL; however, in one of the cases the patient had no known history of any hematologic malignancy.[2]

Furthermore, CLL is associated with a 7.3-fold increased incidence of SCC, in addition to higher recurrence rates of SCC following MMS, and higher rates of skin cancer–related mortality.[1] This is thought to be due to the immunosuppressive effects of CLL; however, patients with CLL are also at increased risk for adverse outcomes during MMS which may contribute to tumor recurrence. A 2-fold increase in subclinical tumor extension, defined as postoperative defect size minus preoperative tumor size, was previously reported when patients with CLL were compared to controls who underwent MMS. The authors noted that this may be due to complication of histologic margin interpretation from dense leukemic infiltrates in CLL.[5]

Distinguishing leukemic infiltrates from reactive inflammatory infiltrates can be challenging and may lead to errors in margin interpretation. Perineural leukemic infiltration may also be present, in a case series by Walther et al[6] of 6 excisional skin cancer specimens in patients with CLL noted a dense, nodular perivascular, periadnexal, and perineural infiltrate in 4 of 6 cases. The presence of leukemic infiltrates may make perineural disease or single-cell spread more difficult to detect, and leukemic infiltration on frozen sections may be erroneously interpreted as perineural spread of a carcinoma.

Immunohistochemical stains can help distinguish between leukemic and reactive infiltrates present during MMS. Leukemic infiltrates are typically CD20+/CD23+/CD5+/CD43+/CD3-. In contrast, benign reactive infiltrates are composed of T-cells that are CD20-/CD23-/CD5+/CD43+.[7] Cytokeratin staining can also be used to evaluate for residual tumor or perineural invasion.[7]

Workup of suspected CLL should include a complete blood count with differential count, peripheral blood flow cytometry, and a peripheral blood smear.[6] CLL is characterized by an absolute peripheral blood B lymphocyte count of $>5 \times 10^9$/L for at least 3 months. Flow cytometry should be ordered to determine the clonality of B cells. Immunophenotyping will show expression of CD5 as well as B-cell antigens CD19, CD20, CD23, and low levels of surface membrane immunoglobulin with either κ or λ light chain expression. Peripheral blood smear will show small, mature lymphocytes with dark staining nuclei and densely condensed chromatin with a narrow rim of cytoplasm. Smudge cells may be seen along with larger, atypical prolymphocytes. Though not necessary for establishing diagnosis of CLL, FISH can be performed on peripheral blood cells to identify chromosomal abnormalities common in CLL.[8]

This case of CLL diagnosed during MMS highlights the increased risk of cutaneous malignancies associated with CLL, as well as the importance of recognizing atypical lymphocytic aggregates on Mohs

sections, and the value of familiarizing oneself with the workup for such a finding.

Conflicts of interest

None disclosed.

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