Primary Cutaneous Anaplastic Large Cell Lymphoma - Long-term Management with Low Dose Methotrexate

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Citation

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Abstract

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INTRODUCTION

Cutaneous CD30+ lymphoproliferative disorders are a rare subtype of primary cutaneous T cell lymphomas (CTCL), representing approximately 25% of all CTCLs. [1] CD30+ cutaneous lymphoproliferative disorders include a spectrum of disease characterized by the proliferation of CD30 expressing lymphocytes in the skin. The lesions typically manifest as red papules, nodules or tumors. In most cases, the CD30+ expressing lymphocytes display an activated T cell phenotype. According to the most recent WHO-EORTC classification, CD30+ lymphoproliferative disorders include primary cutaneous anaplastic large cell lymphoma (CALCL) and lymphomatoid papulosis (LyP). These conditions generally have indolent biological behavior. Clinical and histological correlation in the diagnosis of both CALCL and LyP is essential. Because the biological behavior and treatment differ markedly from the nodal counterpart (nodal anaplastic large cell lymphoma), recognition of CD30+ cutaneous lymphoproliferative disorders and knowledge of appropriate management are critical.

INITIAL PRESENTATION

A 71-year-old man was referred to dermatology for consultation regarding a 2-month history of an enlarging, ulcerated plaque on the right temple (figure 1). Ten months prior to presentation he had developed papulonodules on his scalp which were biopsied and interpreted as an atypical CD30+ lymphoproliferative disorder concerning for anaplastic large cell lymphoma (ALCL). At that time, full body positron emission tomography/computerized tomography (PET/CT) imaging revealed low level abnormal asymmetric increased FDG uptake in the right preauricular region and in the right parotid and submandibular gland regions. No abnormal hypermetabolic FDG uptake was demonstrated on the remainder of the exam. These findings were interpreted as suspicious for a neoplastic process.

The patient had been referred to oncology for management, where the diagnosis of non-Hodgkin lymphoma, stage IE was rendered. He underwent therapy with 3 cycles of rituximab/CHOP. By the end of the treatment course, complete resolution of the scalp lesions was noted, and repeat PET/CT scan was normal. Six weeks after completion of therapy, new scalp nodules were noted. Repeat biopsy revealed a CD30+, Alk-1- negative, CD3+, CD45+, CD20-negative atypical lymphoid infiltrate. This was interpreted by the pathologist as a peripheral T-cell lymphoma of diffuse large cell type, CD30 positive. A subsequent PET/CT scan was again normal.

The patient then underwent local radiation therapy to the temporal/parietal scalp (radiation dose unknown) with complete response. Within 4-6 weeks, a new lesion developed on his face. Histopathology showed changes similar to what had been previously documented. He was then referred to a tertiary center for further evaluation and management. On review of systems he had no fever, chills, night sweats or itching, and his weight had been stable for years. Of note, the patient reported having had 1-2 lesions on his scalp, which had resolved spontaneously within 2 months of onset. His past medical history, surgical history and family history were not significant, with the exception of hypertension, for which he was on amlodipine/benazepril

and benign prostatic hypertrophy, for which he was on tamsulosin.

Figure 1: Cutaneous anaplastic large cell lymphoma: a) ulcerated red plaque on the temple with grossly visible lymphadenopathy; b) lesion close up

Figure 1

Figure 1a

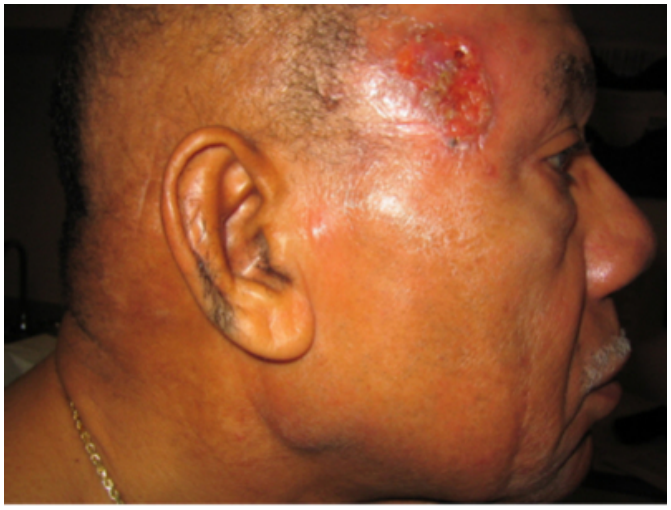
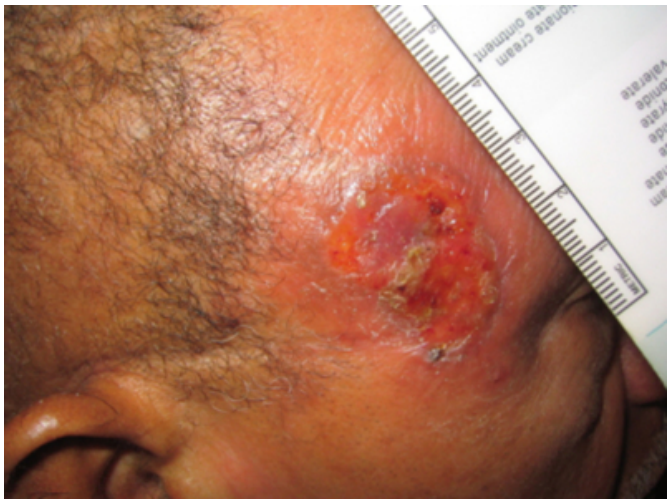


Figure 2

Figure 1b



Physical examination revealed a well-developed, well-nourished male. Vital signs were within normal range; ECOG performance status 0. He had an obvious 3.5-cm by 3-cm ulcerated, erythematous plaque on the right temple (figure 1). Palpably enlarged, mobile nodes were detected in the right pre-auricular and infra-auricular regions; no lymphadenopathy was detected elsewhere on exam.

Laboratory studies including complete blood count (CBC) with differential, lactate dehydrogenase level (LDH), blood T-cell receptor gamma chain gene rearrangement (TCR-gamma) analysis and flow cytometric analysis (leukemia/lymphoma profile) were normal or negative.

CONSIDERATIONS FOR DERMATOLOGIST/ONCOLOGIST FROM REFERRING PHYSICIAN

In this patient, the importance of collaboration by dermatology, oncology and pathology was critical due to the diagnostic possibilities and the differences in therapeutic approach determined by the final diagnosis. Diagnostic considerations included primary nodal lymphoma with regional cutaneous spread, cutaneous CD30+ lymphoproliferative disorder (with reactive lymphadenopathy), CD30+ large cell transformation in a patient with mycosis fungoides (MF), and primary cutaneous CD30+ peripheral T-cell lymphoma (non-anaplastic type). The absence of a clinical history of MF or documented nodal involvement, the history of spontaneously remitting lesions, recurrence after completion of R-CHOP and the skin histopathology supported the diagnosis of CALCL. Lack of appropriate communication among the clinicians and pathologists may have resulted in an unnecessarily aggressive therapeutic intervention.

PATHOLOGY

Several skin biopsies had been obtained throughout this patient's course. Skin histopathology revealed a diffuse dermal lymphocytic infiltrate containing numerous large, pleomorphic lymphocytes (figure 2). The large, atypical lymphocytes were positive for CD3 and CD30 by immunohistochemistry. Immunohistochemistry for Alk-1 protein and epithelial membrane antigen (EMA) was negative. Lesional skin polymerase chain reaction (PCR) based molecular study for a TCR-gamma chain gene rearrangement was positive, supporting the clonal nature of the infiltrate.

Figure 2: Skin histopathology, cutaneous anaplastic large cell lymphoma: a) dense dermal lymphocytic infiltrate composed of large, pleomorphic lymphocytes (hematoxylin and eosin, 40X); b) immunohistochemical stain for CD30 (20X)

Figure 3

Figure 2a

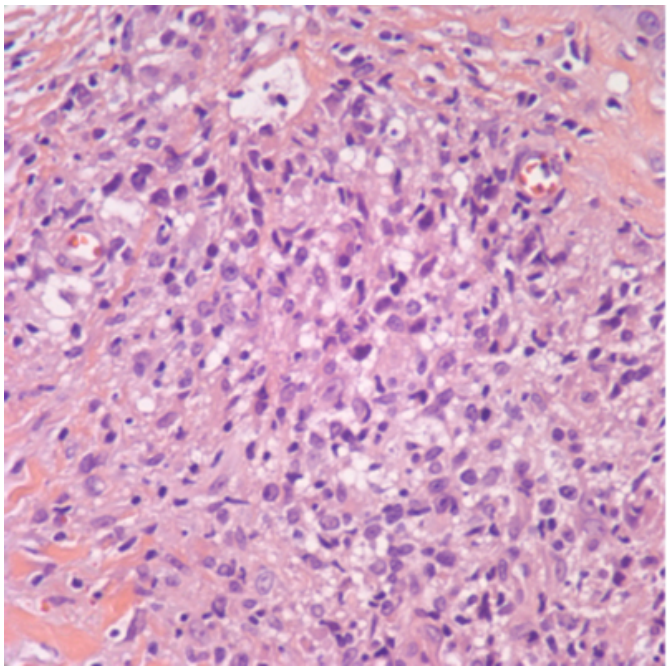
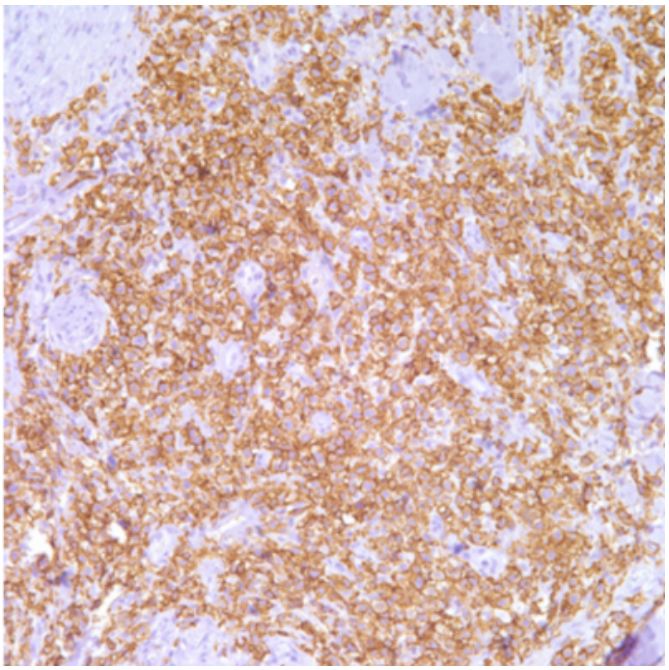


Figure 4

Figure 2b



DIAGNOSIS

Cutaneous CD30+ lymphoproliferative disorder: primary cutaneous anaplastic large cell lymphoma, localized/regional disease. The facial lesion (figure 1) was clinically most suggestive of CALCL, although the possibility of LyP was also entertained in this patient. Because of their overlapping clinical, histological and immunophenotypical features, LyP and CALCL are considered similar diseases at separate ends of the spectrum of CD30+ lymphoproliferative disorders. Differentiation of the two conditions is not always possible at onset of disease. Histology may provide important clues, however, histological findings alone are insufficient to establish the diagnosis; consideration of the clinical context is essential.

STAGING

In contrast to the MF and SS types of CTCL, a standard staging system or TNMB classification system for CD30+ lymphoproliferative disorders does not exist. The applicability of the Ann Arbor system, used for nodal lymphomas, to primary cutaneous lymphomas has been questioned, particularly when patients have disease at multiple skin sites. A TNM classification system was recently proposed for non-MF/SS primary cutaneous lymphomas. This early proposal is likely to undergo revision as more data becomes available, but for now it may serve as a useful guideline for documentation of disease extent in patients with cutaneous lymphomas. [2] In patients with suspected CALCL, systemic evaluation should be performed to exclude the possibility of primary visceral/nodal disease and to evaluate for nodal extension. CBC, LDH level, blood flow cytometry for leukemia/lymphoma panel, and imaging studies (CT w/contrast or PET/CT) are suggested. Although it should be considered, the value of a bone marrow biopsy and aspirate in cutaneous CD30+ lymphoproliferative disorders is unclear.

MANAGEMENT

The European Society of Medical Oncology recently proposed therapeutic recommendations for both LyP and CALCL. [3] Recommendations were stratified based on the presence of solitary (localized) disease versus multifocal lesions. For LyP excision of solitary or localized lesions as first line therapy, with observation as another option, was suggested. For multifocal lesions, observation, phototherapy or weekly methotrexate (~20mg/week) were recommended first line management approaches. Excision or radiation therapy was suggested first line therapy for CALCL (solitary/localized), and methotrexate was first line for multifocal lesions not undergoing spontaneous remission. Several factors were considered in determining the best treatment approach in the patient presented herein, these include:

1) Despite spontaneous regression of some lesions, new lesions continued to develop.

2) Disease recurrence was noted despite treatment with local radiotherapy and R/CHOP.

3) Surgical intervention (excision) was not practical given disease location.

Collaborative, multidisciplinary follow up of this patient is important. Should more widespread cutaneous disease or nodal involvement develop, a change in therapeutic approach would be warranted. [4]

CLINICAL HIGHLIGHTS

CALCL affects adult men more commonly than women, and most patients present with solitary or localized red plaques, papulonodules or tumors. B symptoms are generally absent. Lesion ulceration and regional reactive lymphadenopathy is not uncommon in my experience, as was seen in the patient presented herein. Extracutaneous dissemination is rare and usually involves regional nodes. The majority of patients respond well to therapy, however, a significant percentage of patients have relapses in the skin. Without therapy, most CALCL lesions persist, although a significant percentage regress spontaneously, similar to LyP. LyP usually presents with crops of lesions, several in number but small in size, although the distinction based on size is not always a reliable one. [5] Because histologically LyP and CALCL share similar features, clinical and histological correlation is critical in the diagnosis and management of patients with these CD30+ lymphoproliferative disorders.

TREATMENT GUIDELINES AND SAFETY CONSIDERATIONS

Methotrexate is a chemotherapeutic and immunosuppressive agent that is structurally similar to folate. It is a potent inhibitor of the enzyme dihydrofolate reductase and its ultimate effect is inhibition of cell division. Methotrexate has been used for malignancies (eg. Sezary syndrome) as well as inflammatory disorders (eg. rheumatoid arthritis and psoriasis) for several decades. Chronic low dose oral methotrexate is generally safe and well-tolerated. Concomitant use of oral folate is recommended to reduce select methotrexate related adverse effects. Methotrexate should not be used during pregnancy. Patients on long-term oral methotrexate are generally advised to take the methotrexate in two divided doses one day per week and folate (folic acid) 1-mg daily. The most common adverse effects (AE) include gastrointestinal disturbance such as nausea and anorexia, hepatotoxicity and hematological toxicity. Renal toxicity and idiosyncratic pulmonary toxicity are less common, as is the rare case of immunosuppression related lymphoma that has been reported in individuals with long-term exposure to this drug. Baseline CBC, chemistries, hepatitis A, B and C antibody serologic tests should be obtained. CBC, liver function and renal function studies should be obtained at 1-2 week intervals for several weeks initially, and then periodically (every few months) thereafter. In my experience, when used for cutaneous CD30+ lymphoproliferative disorders, response to treatment with methotrexate is generally rapid. Lesion regression is apparent within the first 4-6 weeks of therapy. Once remission occurs, the patient's dose should be tapered such that the lowest effective weekly dose is administered. Treatment may need to be continued for years.

CONCLUSIONS

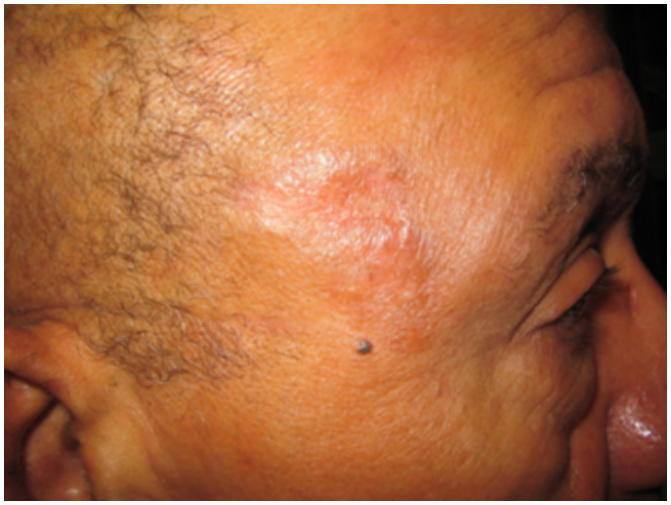
Clinical and pathological correlation is essential in the diagnosis of cutaneous CD30+ lymphoproliferative disorders, including CALCL. Appropriate therapeutic intervention is based on clinical features, including history of spontaneous regression, lesion location and extent of involvement. Most patients with CALCL present with solitary or localized cutaneous disease, and can be managed effectively with excision or local radiotherapy. Cutaneous relapse is common and should not necessarily prompt intervention with aggressive systemic chemotherapy regimens. In some cases, long-term therapy with oral methotrexate is an effective, safe and relatively inexpensive intervention. The overall prognosis of patients with CALCL is excellent, particularly those with solitary lesions or localized disease.

PATIENT FOLLOW-UP

Therapy with oral methotrexate at 15-mg/week (7.5-mg in AM and 7.5-mg in PM one day per week) was initiated. With the exception of mild nausea, the patient experienced no AE (clinical or laboratory). At follow up, three months later, complete clinical remission was noted (figure 3) and the methotrexate dose was decreased to 10-mg/week.

Figure 5

Figure 3: Right temple after 3 months of weekly oral methotrexate



Nine months after treatment was started, the methotrexate dose was again decreased to 5-mg/week. Within 3 months, disease relapse was noted. There was no evidence of nodal involvement at this time. Skin biopsy confirmed disease recurrence. Methotrexate was again increased to 10-mg weekly, with prompt disease remission. The methotrexate has been tapered to 7.5-mg/week and the patient remains free of disease 4 years since diagnosis, and 3 years since commencing methotrexate. To date he has experienced no serious AE of long-term methotrexate use.

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