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Case Report

Bacterial Infection in Ulcerated Tumor in CD8+ Cutaneous T-Cell Lymphoma

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Abstract

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin's T-cell lymphomas that are characterized by a clonal proliferation of T lymphocytes. In the early stages, the course of disease is usually indolent and chronic. In later stages, therapies rarely provide a long-lasting response. CTCL patients have a high incidence of infection and are more likely to die from infections than from CTCL. We present a patient with stage IIB CTCL with a CD8+ phenotype and an infected ulcer with eschar on his right fourth toe and discuss the clinical importance of rapid identification and treatment of infections in patients with CTCL.

ABBREVIATIONS

BID: Two Times Daily; CT: Computed Tomography; CTCL: Cutaneous T-cell lymphoma; MF: Mycosis Fungoides; MRI: Magnetic Resonance Imaging; PO: By Mouth; SS: Sézary Syndrome; SPTCL: Subcutaneous Panniculitis-like T-cell lymphoma; TID: Three Times Daily; TSEB: Total Skin Electron Beam

INTRODUCTION

Cutaneous T-cell lymphomas (CTCL) are a heterogeneous group of non-Hodgkin's T-cell lymphomas that are characterized by a clonal proliferation of T lymphocytes involving skin [1,2]. The most common CTCL are mycosis fungoides (MF), its leukemic variant, Sézary syndrome (SS), and primary cutaneous CD30+ lymphoproliferative; the remaining subtypes account for less than 10% of cases[3,4]. In the early stages, the course of the disease is usually indolent and chronic; however in later stages therapies rarely provide a long-lasting response. Allogeneic hematopoietic stem-cell transplantation is the only potentially curative therapy [5].

CASE PRESENTATION

A 63-year-old white male presented with relapsing stage IIB CD8+ cutaneous T-cell lymphoma. He subsequently developed an infected ulcer where a tumor was present on his fourth right toe.

In 2015, the patient developed an asymptomatic red patch on his left chest. In 2016, a punch biopsy of the chest showed an extensive nodular, perivascular, and panniculitis lymphoid infiltrate of small-to-medium cells with irregular nuclei, condensed chromatin, inconspicuous nucleoli, and scant cytoplasm spanning from the superficial dermis to the subcutis. The lymphoid infiltrate rimmed the individual fat cells. No epidermotropism, foci of large cells, or apoptotic activity were present. The neoplastic cells were positive for CD3 and CD8 and negative for granzyme-B and TIA-1. Clonal expansion of T-cell receptor beta and gamma were present. A biopsy in 2018 showed a predominance of CD8 over CD4, positive CD5, weak labeling of 60-70% of the infiltrate by CD25, and negative CD30 and Epstein-Barr virus-encoded RNA. These findings are consistent with CD8+ CTCL.

The patient's lesions enlarged and raised over time, but cleared with spot radiation (Figure 1 AB). New lesions were treated with topical steroids and oral methotrexate, with continued disease progression. Bexarotene was started at 675 mg but was decreased to 300 mg due to elevated triglycerides. Levothyroxine and fenofibrate were also started for bexarotene-induced central hypothyroidism and elevated triglycerides respectively. The patient was noted to have an ulcer on his right lower extremity (Figure 1C), which improved with total skin electron beam (TSEB) radiation and additional 7 Gy spot treatments (Figure 1D). His disease relapsed with new nodules, tumors, and patches dispersed over his body. With the goal of improvement of disease burden before allogeneic stem cell transplant, the patient was treated under compassionate use with denileukin diftitox, a fusion protein of diphtheria toxin and IL2.

On cycle one, day three of denileukin diftitox, the patient developed a fever of 102.6°F and was later admitted to the hospital; his day four dose of denileukin diftitox was held. Blood and urine cultures were negative, and the white blood cell count and neutrophils were within normal limits. Lactic acid and procalcitonin were both elevated at 2.8 ng/mL (reference range 0.5-2.2) and 0.33 mm (reference range ≤ 0.08) respectively. A chest x-ray showed fullness of the mediastinum and prominent

hila, but a chest CT showed no mediastinal abnormality and no evidence of disease other than focal skin thickening in the posterior lateral chest wall. He was given IV piperacillin/tazobactam and vancomycin and his fever resolved the next morning. The next day, he received his cycle one, day five dose of denileukin diftitox and was discharged without antibiotics.

The following day the patient developed a fever of 100.9°F, which resolved with acetaminophen. Two days later, exam showed that the existing tumor on his right fourth toe had ulcerated (Figure 1E). He was given mupirocin and silvadene for the lesion with betadine soaks and three times daily (TID) dressing changes.

By two weeks later the patient had lost eight pounds and the tumor had progressed. The tumor measured 3 x 3.5 cm with a brown eschar with foul smelling green purulent discharge. Because the Gram stain showed many gram-positive *cocci* in clusters suggestive of *Staphylococcus aureus*; he was empirically started on clindamycin 300 mg TIDby mouth (PO) and ciprofloxacin 500 mg BID PO, with improvement noted two days later. The wound culture grew *Enterococcus faecalis* and coryneform bacteria. The *E. faecalis* was susceptible to ampicillin and vancomycin; the patient was switched to ampicillin 500 mg BID.

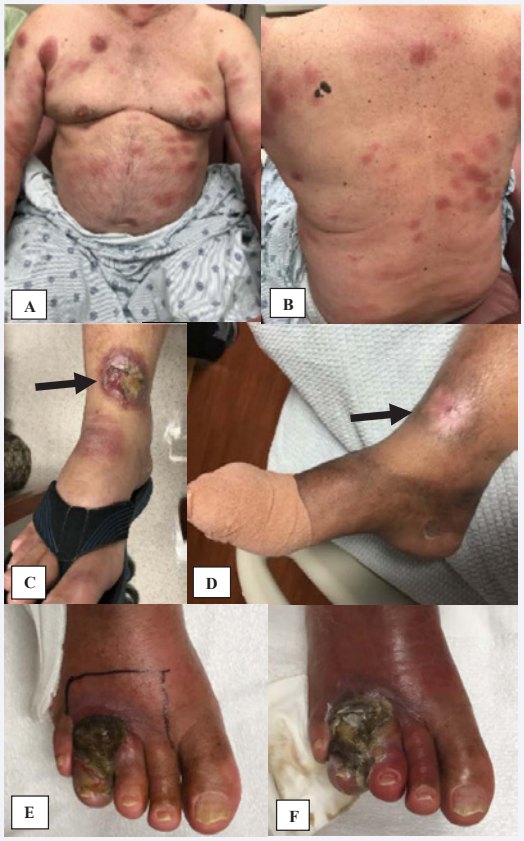

Figure 1 (A) Anterior trunk CTCL lesions (B) Posterior trunk CTCL lesions(C) Right lower extremity ulcer prior to radiation (D) Right lower extremity ulcer after TSEB and spot radiation (E) Ulcer on fourth toe with brown eschar (F) The toe ulcer progressed toward third and fifth toes.

The ulcer continued to progress despite antibiotic therapy. Nine days after the original culture, the infectious disease team was consulted, and a second wound culture was taken. He was started on minocycline 100 mg PO BID, amoxicillin clavulanate 875 mg PO BID, and levofloxacin 500 mg PO daily. The culture grew *Actinomyces neuii* and coryneform bacteria. Magnetic resonance imaging (MRI) of the foot was pended due to the patient's chronically elevated creatinine.

Two weeks later, the patient completed cycle two, day five of denileukin diftitox, which was discontinued for mixed response. The patient was started on TSEB with a plan for 28 Gy total over 14 fractions. However, the lesion continued to progress toward the fifth toe (Figure 1F) and he was admitted for IV piperacillin/tazobactam. MRI of the foot showed edematous changes within the marrow of the fourth toe that were highly suspicious for osteomyelitis. Interventional radiology was consulted but could not find a clean approach for bone biopsy or fluid to drain. A plan was made for possible debridement and to switch to IV ertapenem for six weeks after discharge.

DISCUSSION

While $CD4^+$CTCLs typically have an indolent course, the $CD8^+$ cytotoxic phenotype may be more aggressive, presenting from the onset with widespread plaque- and tumor-stage disease [6]. However, other $CD8^+$subtypes of CTCL, such as hypopigmented MF and subcutaneous panniculitis-like T-cell lymphoma (SPTCL), have a more indolent presentation [7]. A study by Bekkenk et al,. that compared patients with $CD8^+$ and $CD8^-$ phenotypes failed to show a difference in overall survival rates based on CD8 expression alone[8], SPTCL was originally considered in the differential of this patient, but was excluded due to the notable dermal involvement. Similarly, it lacks the epidermotropism of MF. Rather, it represents a hybrid subtype of $CD8^+$ CTCL involving the dermis and subcutis.

CTCL patients have a high incidence of infection, mostly bacterial in origin. Patients with advanced CTCL are more likely to die from infections than from CTCL, possibly due to a compromised skin barrier, a suppressed immune system, or a combination of both [9]. It has been demonstrated that treatment of bacterial infections, most notably *S. aureus*, leads to clinical improvement in CTCL patient [10]. In addition, in our series of ten patients, it was shown that ulcerated lesions with brown to black eschar represent infection with Enterococcus species [11]. These lesions improved with wound care and appropriate antibiotic therapy based on culture results. Of note, our patient presented with tumors and an ankle ulcer prior to treatment with denileukin diftitox. After therapy began, he developed an ulcer with brown eschar on an existing tumor on his right fourth toe. Wound culture of the ulcer was positive for *E. faecalis*, which was treated with ampicillin. It is not clear whether this ulcer is secondary to his CTCL or the denileukin diftitox.

Given the increased susceptibility to infections and potential for disease improvement upon appropriate antibacterial therapy, rapid identification and control of infection are essential. Wound care, whirlpool therapy, bleach baths, chlorhexidine or diluted betadine soaks, and appropriate antibiotics can be used for this purpose [12]. In this case, identification of the osteomyelitis, and

therefore appropriate IV antibiotic therapy, was delayed due to concern for the patient's chronically elevated creatinine. This demonstrates the necessity of increased suspicion for ongoing infections in these patients and the value of early interdisciplinary efforts in navigating infection control and medical comorbidities.

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