CLINICAL VIGNETTE

Primary Cutaneous CD8+ Aggressive Epidermotropic Cytotoxic T-Cell Lymphoma: A Rare Differential for Atypical Psoriasiform Rash

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Case Report

A 69-year-old man with Parkinson's disease was sent to the emergency room from dermatology for further evaluation of worsening full body rash associated with new oral lesions. He initially developed a pruritic, painful, crusted rash to his lower extremities one year prior, and was diagnosed with psoriasis. He was treated with topical mupirocin and high potency topical steroids but the rash progressed to involve the abdomen and upper extremities. One year after onset, he was evaluated by a dermatologist for atypical psoriasis refractory to topical therapy. At that time, punch biopsies showed findings consistent with eosinophilic spongiosus. This histological feature is seen in distinct inflammatory disorders including bullous pemphigoid, pemphigus vulgaris, allergic contact dermatitis, and allergic drug reaction. He was diagnosed with presumed bullous pemphigoid given his clinical picture and history of Parkinson's disease, which is a highly prevalent comorbidity in bullous pemphigoid patients.[1] He started prednisone 20 mg daily, doxycycline, and moderate potency topical steroids. At follow-up two weeks later, minimal improvement was noted, and he received an injection of dupilumab for presumed bullous pemphigoid. Two weeks after the injection, he was reevaluated by his dermatologist with progression of his psoriasiform rash and new onset of oral lesions. He was referred to the emergency department due to concern for Stevens-Johnson syndrome versus erythema multiforme.

Exam in the emergency department revealed erythematous, indurated plaques and nodules scattered on the face, trunk, and upper and lower extremities including the palms and soles with no frank bullae (Figures A-D). Initial evaluation was significant for elevated c-reactive protein (3.4 mg/dl) and lactate dehydrogenase (272 U/L). Methicillin-sensitive Staphylococcus aureus (MSSA) grew from wound cultures. Screening for hepatitis B and C, herpes simplex virus type 1 and 2, syphilis, human immunodeficiency virus, tuberculosis, and human T-lymphotropic virus type 1 and 2 were negative. Punch biopsy from the right arm was performed, and he was started on oral prednisone 60 mg daily as well as topical urea and very high potency topical steroids. In addition, he received cefazolin for MSSA superinfection.

Final pathology and immunohistochemistry from the patient's biopsy returned with a diagnosis of primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL) and oncology was consulted. Additional imaging showed no evidence of lymphoproliferative disease or intrathoracic malignancy. Given the patient's skin findings involved greater than three body regions, he was staged as T3bN0M0B0. Skin-directed therapies included ammonium lactate, clobetasol ointment, tacrolimus ointment, zinc oxide paste, and Aquaphor ointment. Systemic therapies included a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisolone. The first dose of chemotherapy was administered while inpatient and was initially well-tolerated. However, he subsequently developed septic shock with polymicrobial bacteremia. This was likely multifactorial but occurred in the setting of progressive ulcerated back lesions on the back and severe chemotherapy-induced neutropenia (Figures E-F). He was no longer considered for ongoing systemic therapy and eventually discharged home with hospice.

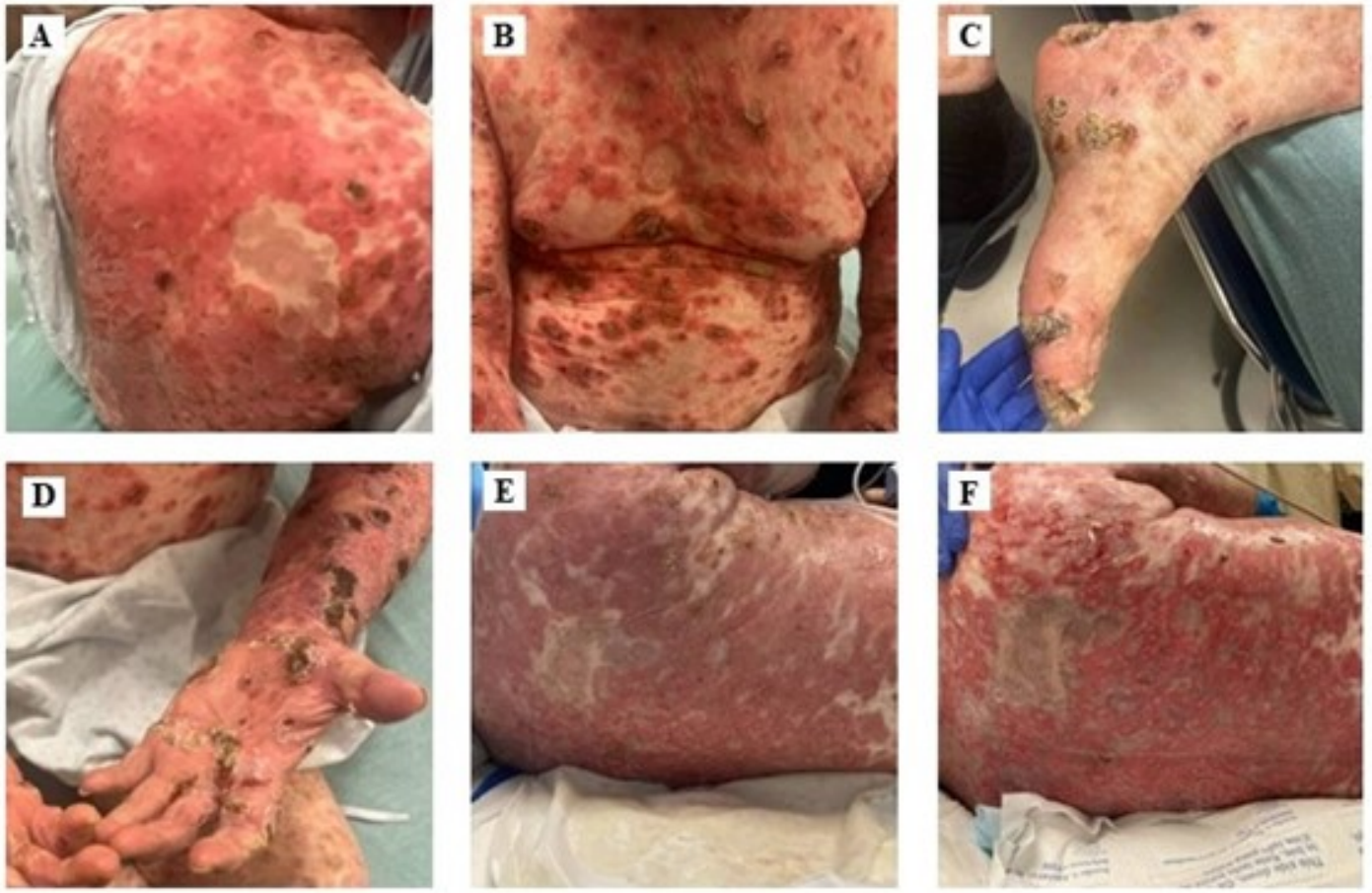

Figure. Clinical features at the time of initial presentation to the emergency department showing erythematous, indurated, confluent plaques and nodules on the (A) back and (B) chest and abdomen. Lesions on the (C) feet and (D) hands and forearms were particularly hyperkeratotic. Lesions on the back became progressively ulcerated at 14 days (E) and 18 days (F) after admission.

Discussion

Primary cutaneous T-cell lymphomas are a heterogenous group of non-Hodgkin lymphomas that are limited to the skin at the time of diagnosis.[2] Among cutaneous T-cell lymphomas (CTCL), primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (AECTCL) accounts for less than 1%.[2] CD8+ AECTCL is characterized by rapidly evolving, extensive annular plaques with erosive features, consistent with the cytotoxic nature of CD8+ T-cells. It is known for an aggressive clinical course and poor prognosis.[3] Given the morbidity, early and accurate diagnosis is important not only to provide appropriate treatment and avoid potentially harmful interventions, but also to engage in early discussions of goals of care.[3]

Skin findings in early CD8+ AECTCL may start with a prodrome of chronic patches prior to developing ulcerative lesions, which can initially resemble an eczematous or psoriasiform rash.[4] In one case series of 30 patients with CD8+ AECTCL, the majority of patients were initially misdiagnosed with benign conditions including psoriasis (11 patients) as occurred in this case, as well as eczema, contact dermatitis, or viral drug eruption.[3] This highlights the importance of reassessment for atypical psoriasiform rashes that are not responding to standard treatment. Certain atypical features may alert the clinician to early CTCL. These include poorly demarcated plaques, in an annular or serpiginous pattern with a central clearing, or asymmetric plaques in sun-protected areas such as the lower trunk, buttocks, and groin.[5]

In atypical or treatment-resistant cases, histopathology is key, including repeat biopsies and additional immunohistochemistry evaluation. Histopathology is required for the diagnosis of CD8+ AECTCL and demonstrates an infiltrate of medium sized atypical lymphocytes involving the epidermal thickness.[3] Immunohistochemistry will show a predominance of CD8+ lymphocytes also positive for CD3 and βF1, as well as at least one of the cytotoxic granules TIA-1, granzyme B, or perforin. Lastly, clonality is demonstrated by TCR-γ rearrangement.[6] Despite characteristic histopathological findings, some authors report early CD8+ AECTCL can present with inconclusive histopathology, which may result in misdiagnosis as atypical psoriasis.[7,8] However, lymphoid rich skin biopsies are not

consistent with psoriasis and should indicate need for additional testing.[3]

Early identification of CD8+ AECTCL may allow the clinician to avoid potentially harmful treatments otherwise indicated for more benign skin conditions. For example, identification of CD8+ AECTCL in early stages can alert physicians to avoid immunosuppressive therapies, associated in several patients with an accelerated course.[3] Recent case reports suggest a possible link between use of immunomodulator dupilumab (a monoclonal antibody against the IL-4 subunit) and subsequent onset of CTCL.[9] One report documented aggressive cytotoxic T-cell lymphoma in a patient on dupilumab for atopic dermatitis.[10] In our case, the patient was treated with prednisone 20mg daily and dupilumab approximately four weeks and two weeks, before he experienced progression of symptoms involving the oral mucosa. A causal link is unlikely as this patient was already presenting with signs of CD8+ AECTCL at the time he received dupilumab. It is possible that this immunomodulator may have accelerated his clinical course.

There are no published clinical trials assessing the treatment of CD8+ AECTCL. However, most patients in case reports have received both skin-directed and systemic regimens.[3] Systemic therapy often includes chemotherapeutic regimens used for peripheral T cell lymphoma, including doxorubicin-based regimens (cyclophosphamide, doxorubicin, vincristine, and prednisone).[6] Unfortunately, because of the aggressive nature of CD8+ AECTCL, there is often poor response to treatment, with a median survival of less than two years and average five-year survival of 18%.[6] Prior reports suggest that loss of CD2 and CD5 T-cell markers may be indicative of rapidly progressive disease, as with for the patient presented here. Others with CD7-/CD2+ phenotypes may have a more chronic disease course.[6]

While there is no evidence that early intervention will prevent the development of extensive ulcerations associated with high morbidity and mortality in CD8+ AECTCL, early diagnosis is still important.[6] This allows earlier engagement with patients regarding goals of care. Early goals of care discussions have been associated with increased goal-congruent care with decreased rates of re-hospitalization.[11] Given the aggressive course of CD8+ AECTCL, early diagnosis and initiation of goals of care discussions meaningfully impact patients' quality of life and end-of life care.

Our patient illustrates challenges inherent to early and accurate diagnosis of CD8+ AECTCL, which require understanding of clinical, histopathological, and immunotypic findings. It is important for clinicians to recognize that CD8+ AECTCL can initially present with a psoriasiform rash which does not respond to usual treatments. This should prompt re-examination of histopathology and additional immunohistochemistry testing. Although there is limited evidence that early intervention can prevent morbidity or mortality related to CD8+ AECTCL, it allows for earlier patient-centered discussions aimed at prioritizing patients' goals as well as identification of patients that should avoid immunosuppressive therapies, which may accelerate the course.

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