

# Collisional variant of CD8<sup>+</sup> mycosis fungoides and indolent CD8<sup>+</sup> lymphoid proliferation



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## INTRODUCTION

CD8<sup>+</sup> lymphoid infiltrates of the skin remain a poorly understood heterogeneous group of disorders with variable prognosis. There are several subgroups of primary cutaneous CD8<sup>+</sup> T-cell lymphoma: (1) CD8<sup>+</sup> mycosis fungoides (MF), (2) CD8<sup>+</sup> variants of CD30<sup>+</sup> lymphoproliferative disease<sup>1</sup>; (3) aggressive epidermotropic cytotoxic CD8<sup>+</sup> T-cell lymphoma, (4) subcutaneous panniculitis-like T-cell lymphoma, (5) indolent CD8<sup>+</sup> lymphoid proliferation (usually of the face), (6) CD8<sup>+</sup> variants of  $\gamma/\delta$  T-cell lymphoma and natural killer T-cell lymphoma, and (7) peripheral T-cell lymphoma not otherwise specified predominated by large atypical CD30<sup>-</sup> T cells (Table 1). Recognition of these subtypes is crucial for accurate prognostication and treatment. CD8<sup>+</sup> MF is the most common of these groups. We present a case of CD8<sup>+</sup> cutaneous T-cell lymphoma exhibiting features of CD8<sup>+</sup> plaque-stage MF and an indolent CD8<sup>+</sup> lymphoid proliferation, likely deriving from the same neoplastic clone. The unusual cytomorphologic features of this case represent a novel pattern of CD8<sup>+</sup> T-cell lymphoma.

## CASE REPORT

A 42-year-old man presented with a brown plaque on his thigh present for 1 year. Within the last several months, the lesion thickened and grew in size but remained asymptomatic. On physical examination, there was a 16- × 16-cm dusky red thick plaque, bordering on tumor, with scale on the right posterior thigh. Other cutaneous findings included a 1- × 1-cm scaly erythematous patch on the abdomen and scattered hypopigmented patches and thin pink plaques on the buttocks, back, and lower extremities (Fig 1). The hypopigmented

### Abbreviation used:

MF: mycosis fungoides

patches were present for many years before development of the plaque. He had 2% total body surface area patch involvement and 0.5% total body surface area plaque, consistent with stage 1A MF.

Biopsy specimens were obtained from the hypopigmented patch on the buttock and the thigh plaque. The hypopigmented patch showed typical paucicellular CD8<sup>+</sup> epidermotropic infiltrate, characteristic for hypopigmented MF (not shown).

The larger indurated plaque showed classic features of MF similar to his other biopsy, but there was also a deeper-seated extensive tumefactive diffuse and nodular lymphocytic infiltrate (Fig 2). Regarding the more superficial classic MF component, an epidermotropic and superficial band-like infiltrate of small- to intermediate-sized cerebriform lymphocytes were observed (Fig 3). There was no anagiodestruction and minimal epithelial injury.

However, the deeper-seated component appeared to be composed of cells with a very different cytomorphology from the classic cerebriform component typical for MF noted superficially. The cells had round nuclei, small basophilic nucleoli, and eosinophilic rims of cytoplasm with eccentric disposition of the nucleus imparting a somewhat monocytoid appearance to the cells, although clearly, phenotypically the cells were of T-cell lineage (Fig 4).

Immunohistochemically, the superficial epidermotropic component exhibited immunoreactivity for the pan T-cell markers CD2 and CD3; however, there was a significant reduction in the staining for

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**Table I.** Cytotoxic markers in CD8<sup>+</sup> lymphoid infiltrates in descending order of frequency

	Clinical features	Cytotoxic markers
CD8 <sup>+</sup> MF	Previous or concurrent presence of patch or plaque-like lesions.	$\beta$ -F1 <sup>+</sup> , CD8 <sup>+</sup> , $\gamma/\delta$ <sup>-</sup>
CD30 <sup>+</sup> lymphoproliferative disorders	Spectrum of CD30 <sup>+</sup> lymphoproliferative disorders encompasses lymphomatoid papulosis, primary cutaneous anaplastic large cell lymphoma, and systemic anaplastic large cell lymphoma with skin involvement.	CD30 <sup>+</sup> , CD8 <sup>+</sup> (although most CD30 <sup>+</sup> lymphoproliferative disorders are commonly derived from CD4 <sup>+</sup> cells), CD3 <sup>+</sup> . Significant epidermotropism in some cases. Granzyme positivity can be observed. CD56 can be positive. TIA <sup>+</sup> in some cases. <sup>1</sup>
Subcutaneous panniculitis-like T-cell lymphoma	Nodular skin lesions most frequently located on the legs	CD8 <sup>+</sup> , TIA-1 <sup>+</sup> , granzyme B <sup>+</sup> , perforin positive. Restricted to subcutis, and epidermotropism is absent.
CD8 <sup>+</sup> variant of $\gamma/\delta$ T-cell lymphoma	Rapidly progressing, disseminated plaques or ulceronecrotic nodules or tumors. Mucosal and extranodal surfaces frequently involved.	TCR $\gamma/\delta$ <sup>+</sup> , $\beta$ -F1 <sup>-</sup> , CD3 <sup>+</sup> , CD2 <sup>+</sup> , CD5 <sup>-</sup> , CD56 <sup>+</sup> , CD8 <sup>+</sup>
Primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma	Localized or disseminated papules, nodules, and tumors with ulceration and necrosis. Progresses rapidly over months to include visceral sites sparing the lymph nodes.	CD8 <sup>+</sup> , $\beta$ -F1 <sup>+</sup> , CD8 <sup>+</sup> , granzyme B <sup>+</sup> , perforin <sup>+</sup> , TIA-1 <sup>+</sup> , CD45RA <sup>+/-</sup> , CD45RO <sup>-</sup> , CD2 <sup>-/+</sup> , CD4 <sup>-</sup> , CD5 <sup>-</sup> , CD7 <sup>+/-</sup>
Indolent CD8 <sup>+</sup> lymphoid proliferation	Solitary lesion most commonly at acral sites (particularly on the ear).	CD3 <sup>+</sup> , CD4 <sup>-</sup> , CD8 <sup>+</sup> , TIA-1 <sup>+</sup> , granzyme B <sup>-</sup> , CD30 <sup>-</sup> . CD68 often shows positive Golgi dot-like staining. Loss of pan-T-cell antigens (CD2, CD5, CD7), low proliferation rate.
Peripheral T-cell lymphoma not otherwise specified with CD30 <sup>-</sup> large cells	Patients present with generalized lymphadenopathy with or without extranodal disease. The skin and gastrointestinal tract are the most commonly involved extranodal sites.	Heterogenous group of malignant T cells with varying histology. T-cell-associated antigens are variably expressed (CD3 <sup>+/-</sup> , CD2 <sup>+/-</sup> , CD5 <sup>+/-</sup> , CD7 <sup>+/-</sup> ). Rare tumors may express CD20. Most are $\alpha/\beta$ TCR <sup>+</sup> ; rare are $\gamma/\delta$ TCR.

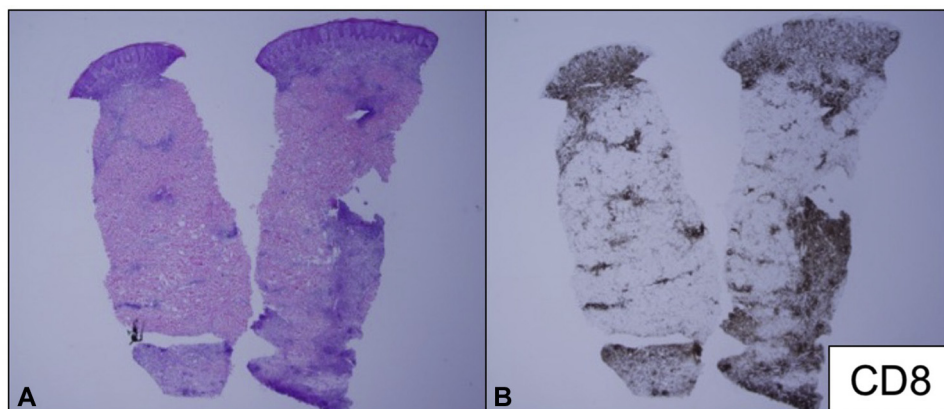
**Fig 1.** Red dusky plaque on the right posterior thigh with scattered hypopigmented patches and plaques on the buttocks and posterior thighs.

both CD5 and CD7. The cells were CD8<sup>+</sup> and exhibited expression cytotoxic proteins granzyme and TIA. The deeper-seated disparate noncerebri-form component showed a similar CD8<sup>+</sup> phenotype with loss of CD5 and CD7, but the cells also showed a perinuclear dot-like staining pattern for CD68 (Fig 4).

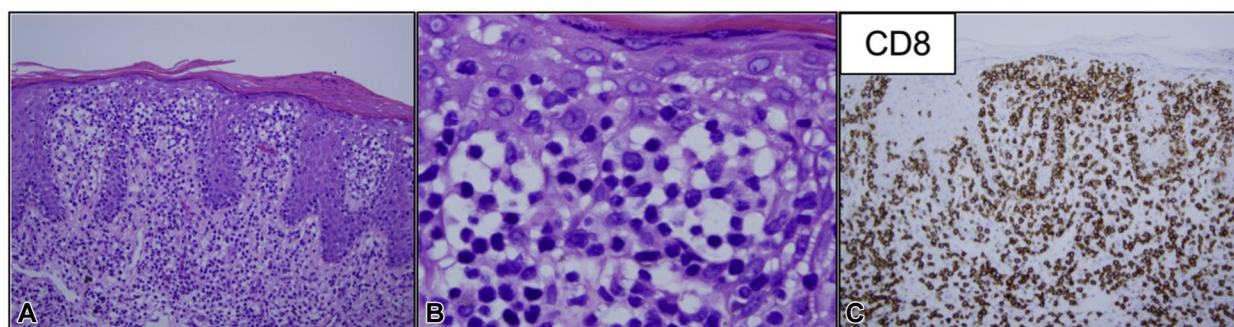
Peripheral flow cytometry showed no morphologic or immunophenotypic evidence of T-cell lymphoma, and molecular studies were negative for T-cell receptor gene rearrangement. After clinicopathologic correlation, the patient was referred for treatment with localized radiation therapy to the affected area on the posterior thigh, which led to complete clearance of the plaque. Narrow-band ultraviolet B radiation led to complete clearance of the hypopigmented patches with 3 years of follow-up.

## DISCUSSION

Primary CD8<sup>+</sup> cutaneous T-cell lymphoma represent a disease spectrum with variable presentations.



**Fig 2.** **A**, Hematoxylin-eosin stain shows an atypical epidermotropic and deeper-seated nodular lymphocytic infiltrate. **B**, Immunohistochemical analysis shows positive immunoreactivity of CD8 throughout the infiltrate. (Original magnifications:  $\times 2$ .)



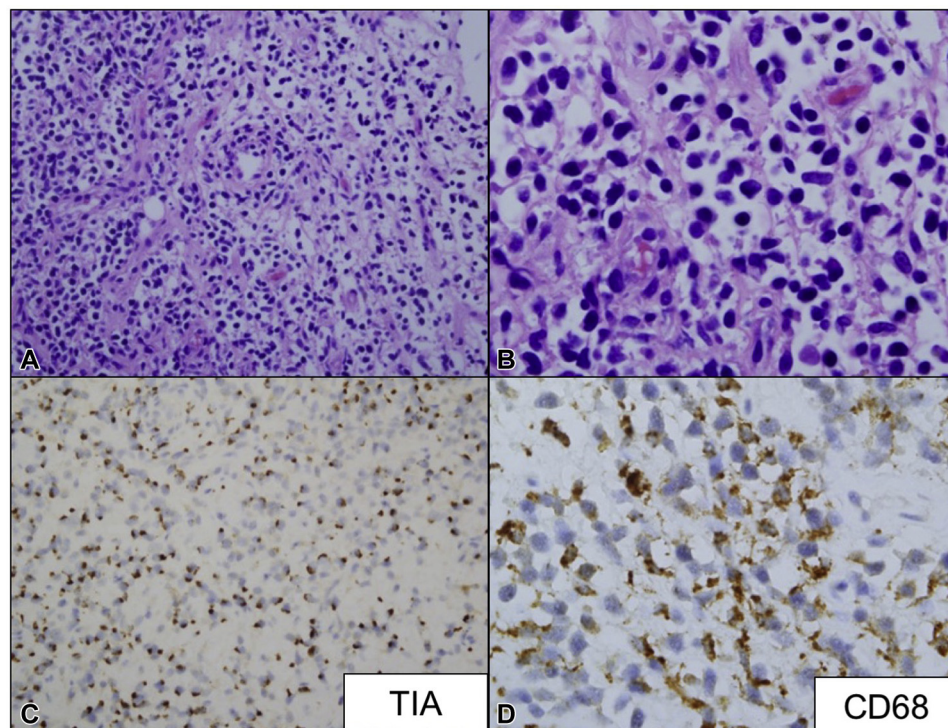
**Fig 3.** **A**, Hematoxylin-eosin stain shows atypical epidermotropic lymphocytic infiltrate and **B**, atypical cerebriform lymphocytes at the epidermal-dermal interface. **C**, Immunohistochemistry shows CD8 positivity. (Original magnifications: **A** and **C**,  $\times 20$ ; **B**,  $\times 100$ .)

We present a case of classic CD8<sup>+</sup> patch and plaque stage MF associated with a tumorous infiltrate of neoplastic CD8 T cells that showed light microscopic and phenotypic features typical for indolent CD8<sup>+</sup> lymphoid proliferation and not tumor stage MF. In particular, the deeper-seated neoplastic CD8<sup>+</sup> T-cell infiltrate would have been expected to represent tumor stage MF; however, the noncerebriform and distinctly monocytoid cytomorphology along with the dot-like staining pattern around the nucleus for CD68 defined a morphology and phenotypic profile held to be diagnostic of indolent CD8<sup>+</sup> lymphoid proliferation.

CD8<sup>+</sup> indolent lymphoid proliferation of the skin was first described in the context of 4 patients presenting with solitary lesions on the ear exhibiting a tumefactive nonepidermotropic small noncerebriform CD8<sup>+</sup> T-cell infiltrate.<sup>2</sup> Subsequent to that description, other similar cases, but at different sites, have been reported including solitary lesions involving the nose, eyelid, and acral surfaces.<sup>3-5</sup> The patient described here is different from other

previously reported cases due to the novel site involvement and background of MF. The fact that the patient had an excellent response to radiotherapy for this one isolated area and has not had other tumorous lesions would certainly point to a diagnosis of indolent CD8<sup>+</sup> lymphoid proliferation, although developing in the context of MF.<sup>6</sup> There is literature precedent on divergent morphologies developing in the setting of an established hematologic malignancy in which commonality of neoplastic clones are best exemplified by Richter transformation in the setting of chronic lymphocytic leukemia or histiocytic in the setting of follicular B-cell lymphoma.<sup>7</sup>

Aggressive epidermotropic cytotoxic CD8-positive T-cell lymphoma can be considered in the differential diagnosis of an epidermotropic neoplastic T-cell process with significant tumefactive dermal involvement. However, neither the clinical presentation or light microscopic findings supported this diagnosis.<sup>8</sup> Patients with aggressive epidermotropic cytotoxic CD8-positive T-cell



**Fig 4.** **A and B**, Hematoxylin-eosin stain shows that the tumefactive deeper seated proliferation of lymphocytes had a distinctly atypical noncerebriform appearance. **C**, Immunohistochemical analysis with positivity for CD8 (not illustrated) TIA and **D**, CD68 in a distinct perinuclear Golgi staining pattern. (Original magnifications: **B** and **D**,  $\times 100$ ; **C**,  $\times 40$ .)

lymphoma present with widespread ulcerative patches, plaques, papules, and nodules with necrosis. Pathology shows striking epidermotropism of atypical  $CD8^+/CD4^-$  noncerebriform lymphocytes showing a naïve  $CD45RA$  phenotype with cytotoxic protein expression and a high Ki-67 proliferation index. There is also a proclivity for vascular invasion leading to vascular thrombosis and secondary ischemic alterations.<sup>9</sup> In this case, the protracted history of patches over years in concert with the epidermotropic cerebriform lymphocytic infiltrate unaccompanied by angiodesstructive features were so typical of MF that the diagnosis of aggressive epidermotropic cytotoxic CD8-positive T-cell lymphoma is not a realistic consideration.<sup>9</sup>

One of the key points of presenting this case is that recognition of this rare divergent morphology capturing 2 distinctive  $CD8^+$  cutaneous lymphoid neoplasms resulted in implementation of less aggressive therapy than what would have been given for tumor stage MF.

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