Rapidly progressive hyperpigmented keratotic plaques with epidermotropism

A 47-year-old, otherwise healthy man presented with multiple hyperpigmented plaques on his trunk and extremities. The plaques were first noticed on the trunk five months back which subsequently involved the extremities. He had no systemic complaints. On cutaneous examination, we noted numerous round-to-oval hyperpigmented keratotic papules and mildly scaly plaques (size 1-5 cm) on the trunk and extremities [Figure 1a]. The truncal and lower limb plaques were larger, with some showing superficial ulceration and annular configuration [Figure 1b]. There was prominent palmoplantar involvement, with coalescing keratotic papules and plaques on the soles [Figure 1c]. Routine laboratory investigations including complete blood count, serum biochemistry and lactate dehydrogenase levels (143 U/L) were within normal limits. A punch skin biopsy was performed from keratotic plaques over the abdomen and sole.

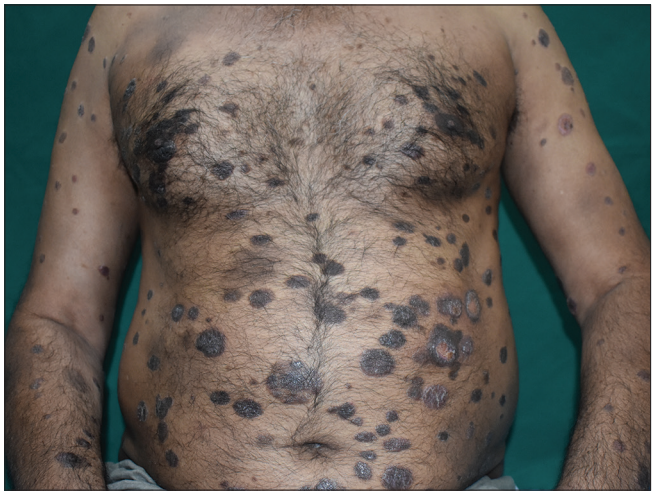

Figure 1a: Hyperpigmented papules and plaques on the trunk. Some plaques show central ulceration

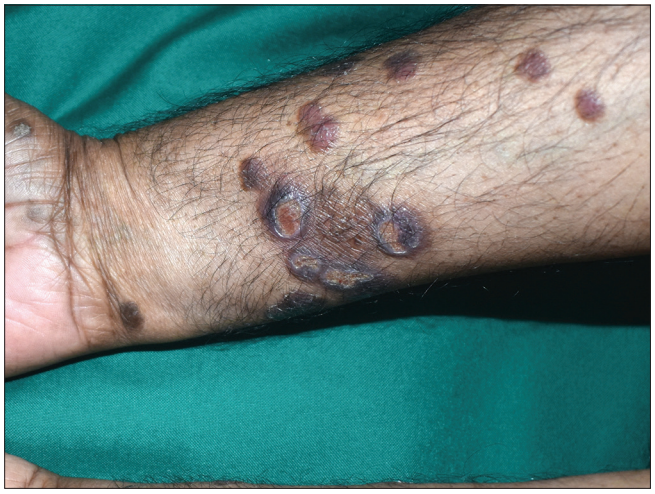

Figure 1b: Ulcerated plaques arranged in an annular configuration around a resolving plaque

Question

What is your diagnosis?

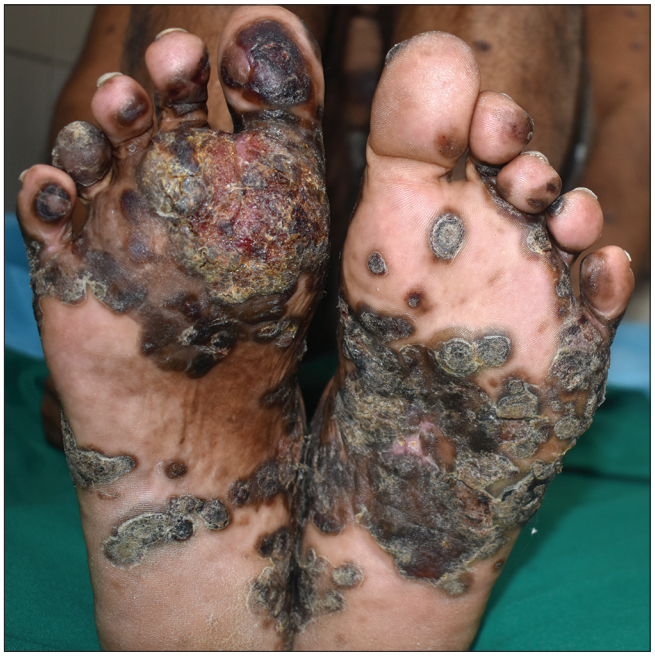

Figure 1c: Confluent plaques over bilateral soles; few plaques on the right sole are ulcerated

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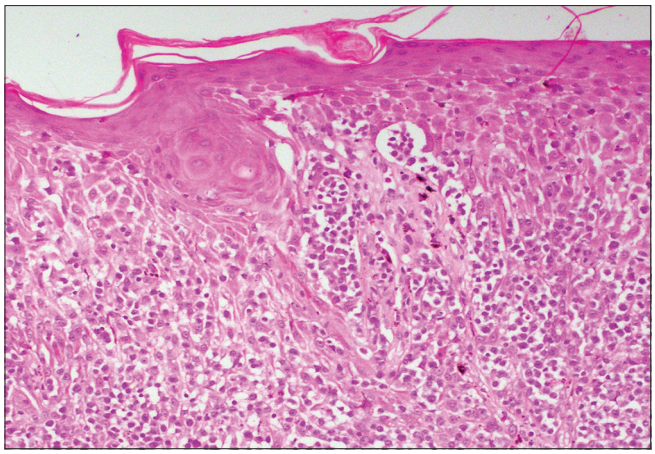

Figure 2a: Skin biopsy from abdomen showing lymphocytes in the epidermis, both singly and in a few clusters, with minimal spongiosis (epidermotropism) (hematoxylin and eosin, ×100)

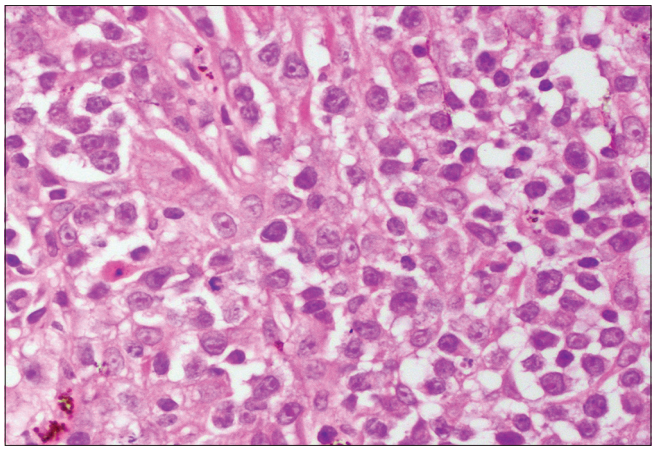

Figure 2b: Higher magnification shows the lymphocytes to be large, pleomorphic and atypical; a necrotic keratinocyte is also visible (hematoxylin and eosin, ×400)

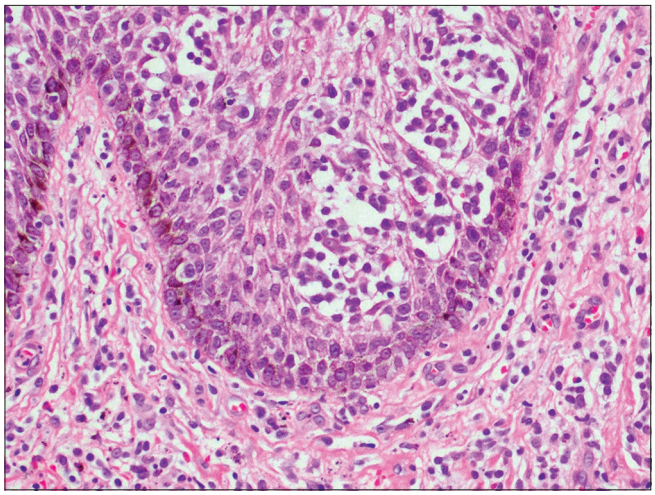

Figure 2c: Skin biopsy from sole shows clusters of atypical lymphocytes (Pautrier microabscesses) in the epidermis (hematoxylin and eosin, ×200)

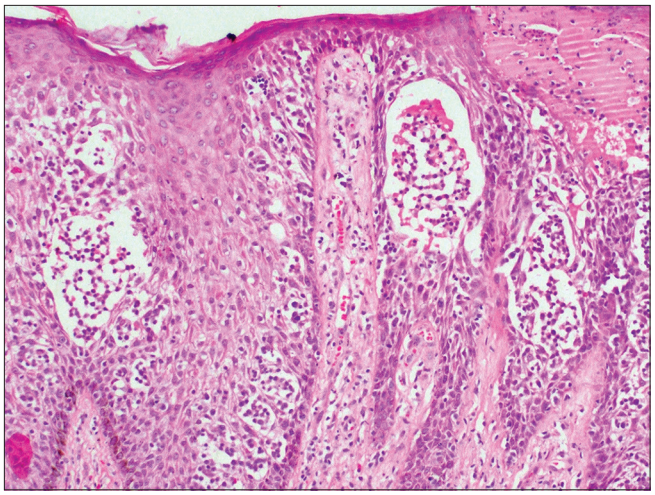

Figure 2d: Another focus from the same biopsy shows epidermal spongiosis with spongiotic blisters as well as lymphocyte epidermotropism (hematoxylin and eosin, ×100)

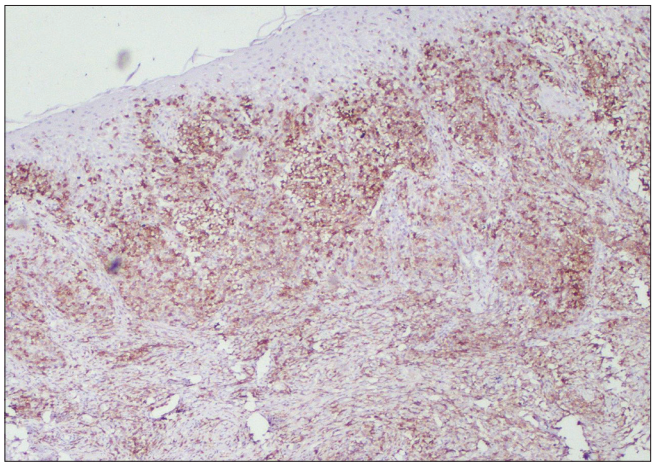

Figure 3a: Immunohistochemistry showing strong CD8 expression in lymphocytes (×40)

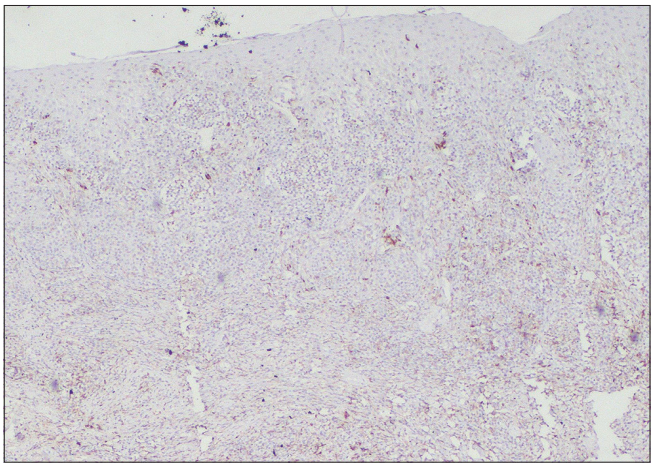

Figure 3b: Immunohistochemistry showing focally positive CD4 lymphocytes (×40)

Answer

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma

Discussion

Skin biopsies showed irregularly acanthotic epidermis with dense diffuse pan-dermal infiltrate of lymphocytes and histiocytes. There were scattered large and atypical lymphocytes in the epidermis, present singly and in clusters forming microabscesses [Figures 2a and b]. We observed mild-to-moderate epidermal spongiosis and focal spongiotic vesicles, along with few necrotic keratinocytes [Figures 2c and d]. The lymphocytes were strongly immunopositive for CD3 and CD8 [Figure 3a], focally positive for CD4 [Figure 3b] and negative for CD20 and CD30. Peripheral blood examination and bone marrow biopsy were unremarkable. 18-fluorodeoxyglucose whole body positron emission tomography scan demonstrated metabolically active uptake limited to cutaneous and soft-tissue lesions. The patient was treated with methotrexate (15–30 mg/week) for three months, followed by all-trans-retinoic acid (80 mg/day) for a month without much improvement. Subsequently, pegylated doxorubicin (50 mg/month) was administered with partial flattening of the plaques. Six months following treatment, the disease worsened with multiple new plaques and new-onset bullous lesions and crusted erosions, with immunohistological features of aggressive epidermotropic CD8+ T-cell lymphoma. He was subsequently administered one cycle of gemcitabine (1.2 g/m^2) and oral prednisolone 40 mg/day, however, COVID-19 lockdown prevented further follow-up visits. We lost the patient after three months due to worsening of skin lesions and general condition.

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma represents less than 1% of all cutaneous T-cell lymphomas and is included as a provisional entity in the latest WHO/EORTC classification.[1] It was referred to as "Berti's lymphoma," "generalized pagetoid reticulosis," or "Ketron-Goodman disease" before the category of primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma was established.[2-4] It is characterized by rapidly progressing disseminated patches, papules, plaques, nodules and tumors with central necrosis and ulceration.[4] There is a propensity for visceral metastasis to lung, testis, central nervous system and oral mucosa, but lymph nodes are often spared. However, skin-limited disease has been reported rarely, similar to our case.[5] Histological features include dense dermal lymphocytic infiltrates, with marked pagetoid epidermotropism composed of pleomorphic small- to medium-sized T-cells. The neoplastic T-cells have a CD8+/CD4- cytotoxic T-cell profile with granzyme B, perforin and TIA-1 marker expression.[6] Conventional therapies for cutaneous T-cell lymphomas are generally ineffective, while interferon-alpha and multiagent chemotherapy have been tried with unsatisfactory results.[7,8] It has an aggressive clinical course and poor prognosis with a median survival of 12–32 months.[4,7] Allogenic hematopoietic

Table 1: Differences between primary cutaneous aggressive epidermotropic CD8+ T-Cell lymphoma and CD8+ mycosis fungoides

Features	Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma	CD8+ mycosis fungoides
Clinical features		
History	Short, weeks to months, rapid progression	Long, months to years
Course	Aggressive; rapidly fatal course with a median survival time of 12–32 months	Indolent
Morphology of skin lesions	Patches, plaques, verrucous or hemorrhagic papules, nodules and tumors A few show annular plaques with peripheral erosions and central ulceration; some may show a spontaneous central resolution	Patches, plaques and nodules
Distribution of skin lesions	Generalized Acral accentuation	Photocovered area
Progression	No sequential progression from patches to plaques to nodules	Sequential progression from patches to plaques to nodules noted
Mucosal involvement	Common	Rare
Metastasis	Common, early Spares lymph nodes Involves lung, testes, CNS and oral cavity	Rare, late Usually nodal Rare extranodal; spreads to lung, spleen and liver
Histopathology		
Epidermotropism	All stages show marked epidermotropism and it usually follows a pagetoid or linear pattern	Less pronounced, usually present in early lesions
Spongiosis	Usually seen, sometimes prominent with spongiotic vesicles	Rare
Necrotic keratinocytes	Quite common	Rare
Pautrier microabscess	Common, with large intraepidermal aggregates of atypical lymphocytes	Less common and scattered microaggregates of atypical lymphocytes
Depth of infiltrate	Nodular or diffuse infiltrate extending to deep dermis or subcutis	Superficial dermal infiltrate
Adnexae	Usually involved (lymphoepithelioid pattern)	Rarely affected, seen in syringotropic and folliculotropic variants
Angiocentricity and angioinvasion	Relatively common	Very rare
Immunophenotyping	CD2–, CD4–, CD5–, CD45RO– CD3+, CD7+, CD8+, CD45RA+ βF-1+, TIA-1+, perforin+, granzyme-B+ commonly positive High Ki-67	CD4±, CD7–, CD45RA± CD2+, CD3+, CD5+, CD8+, CD45RO+ TIA-1±, perforin±, granzyme-B± uncommon
Treatment		
Conventional therapy (skin-directed treatment/low-dose methotrexate)	Ineffective	Usually first line of treatment
Multiagent chemotherapy	Usually required, though not effective Allogenic hematopoietic stem cell transplantation	Rarely needed

βF-1: Beta-factor-1, TIA-1: T-cell intracellular antigen-1

stem cell transplantation has induced partial or complete remission in few patients.[4] A recent report has highlighted long-term remission with brentuximab vedotin monotherapy.[9] In the absence of a standard accepted treatment for this lymphoma and skin-limited disease in our patient, we tried methotrexate initially, but later escalated to monoagent chemotherapies such as doxorubicin and gemcitabine due to inadequate response.

Apart from primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma, differential diagnoses of CD8+ lymphoproliferative disorders include CD8+ mycosis fungoides, pagetoid reticulosis, lymphomatosis papulosis type D, primary cutaneous acral CD8+ lymphoma and subcutaneous panniculitic T-cell lymphoma. Of these, CD8+ mycosis fungoides particularly can be a close differential diagnosis due to its clinical and histologic similarity (epidermotropism). Although both can present with plaques and ulcerated tumors, the verrucous or hyperkeratotic and annular morphology of plaques, accentuated palmoplantar involvement and rapid disease progression favour the diagnosis of primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma. On histopathology, features such as spongiosis with spongiotic blisters, necrotic keratinocytes, deep dermal infiltrate, angio- and adnexotropism in addition to epidermotropism should raise the possibility of primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma [Table 1]. It is not unusual for these patients to be initially misdiagnosed as mycosis fungoides.[4] Correct diagnosis of this aggressive lymphoma requires a strong clinicopathological correlation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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