Primary cutaneous CD8+ aggressive epidermotropic T-cell lymphoma mimicking pyoderma gangrenosum

Sir,

A 62-year-old male was admitted to a hospital in Australia with acute worsening and secondary infection of a non-healing cutaneous ulcer on the right hip [Figure 1a]. The ulcer had been present for nearly one year with no history of constitutional symptoms such as fever, weight loss or night sweats, diabetes, immunosuppression or recent travel.

Skin biopsy from the ulcer demonstrated a non-specific inflammatory exudate with necrosis extending to the subcutis. *Pseudomonas aeruginosa* was identified on tissue culture. He was treated with intravenous gentamicin and surgical wound debridement for the bacterial wound infection following which the hip ulcer rapidly expanded [Figure 1b]. A revised diagnosis of pyoderma gangrenosum was made on clinical grounds, suspecting 'pathergy'. Over the next four months, the patient received multiple systemic immunosuppressive agents for presumed pyoderma gangrenosum including oral prednisone 50 mg daily for two weeks, hydroxychloroquine 200 mg twice a day for six weeks and mycophenolate mofetil 1000 mg twice a day for six weeks [Table 1], with no response. In addition, he also developed new hyperkeratotic plaques on his torso, limbs and scalp some of which rapidly broke down and ulcerated [Figure 1c].

Fresh deep incisional biopsies were taken from the new ulcers on the right axilla and thigh. Histopathology of the biopsies demonstrated ulceration of the epidermis with a prominent, predominantly lymphocytic, lichenoid inflammatory infiltrate in the surrounding superficial dermis. An interface reaction was present at the dermoepidermal junction [Figure 2a] with lymphocytic exocytosis. This infiltrate consisted primarily of CD3+ T-cells with a greater proportion CD8+ cells [Figure 2b] compared to CD4+ [Figure 2c]. There was also an aberrant loss of staining of the T-cell marker CD5 in a subset of T-cells [Figure 2d]. Furthermore, there was negative

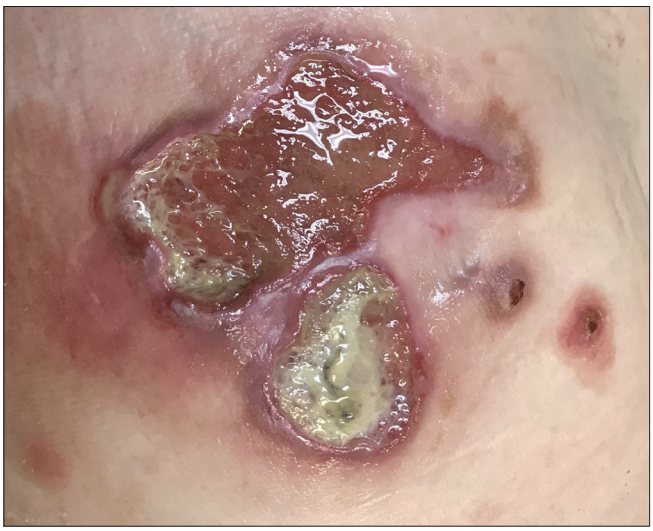

Figure 1b: Rapid expansion of ulcerated plaque shortly after biopsy

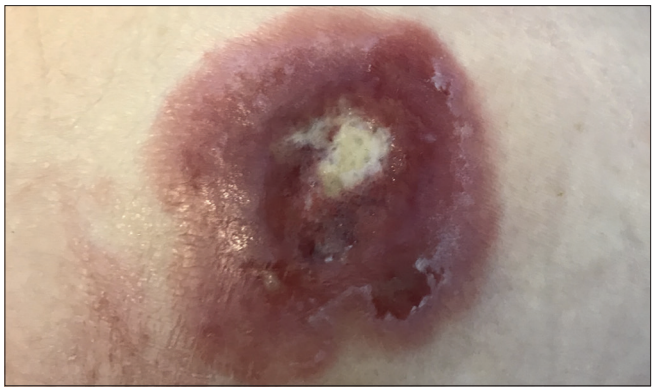

Figure 1a: Ulcerated erythematous plaque over right hip

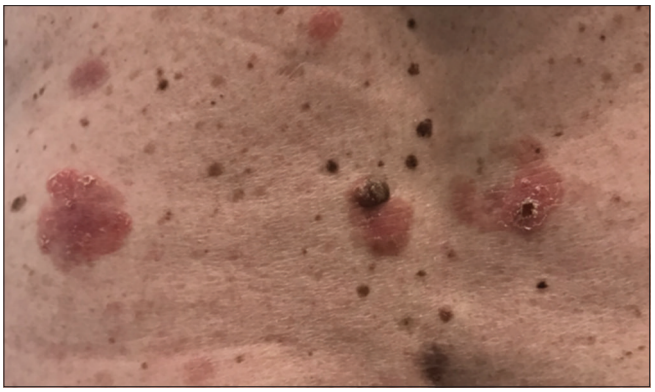

Figure 1c: Development of multiple plaques with hyperkeratosis and crusting on the back of the patient

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staining for CD56, ALK and EBER, some positive staining for CD30, CD20, granzyme B and perforin in scattered cells, and Ki-67 staining in approximately 80% of lymphoid cells. The overlying epidermis showed prominent spongiosis with occasional apoptotic keratinocytes. These features were consistent with a diagnosis of cutaneous T-cell lymphoma ($CD8^+$ cytotoxic T-cell phenotype), although further specification of a subtype required further clinical correlation.

Given the combination of multiple new hyperkeratotic plaques that rapidly ulcerated, an absence of erythematous patches and the presence of the above-mentioned histological features, a diagnosis of primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (PCAE) was established.

After urgent haematology review, and a positron emission tomography scan that demonstrated no extracutaneous activity, the patient was commenced on six cycles of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy followed by weekly methotrexate. Though there was an initial rapid healing of all cutaneous ulcers including the right hip [Figure 3], relapse occurred three months after completion of chemotherapy. Following this, the patient was put on pralatrexate, although remission was not successfully achieved, and an alternative chemotherapy agent is now being sought.

In retrospect, the key difficulty in this case was determining whether the initial right hip ulcer represented primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, or pyoderma gangrenosum secondary to malignancy, given the non-diagnostic histopathological features seen on initial biopsy. However, there are a few reasons why cutaneous lymphoma should be the favoured diagnosis of the initial ulcer. First, there was a high degree of necrosis and ulceration on the initial biopsy, making it difficult to appreciate histological changes of lymphoma. A previous case report has also described a primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma ulcer

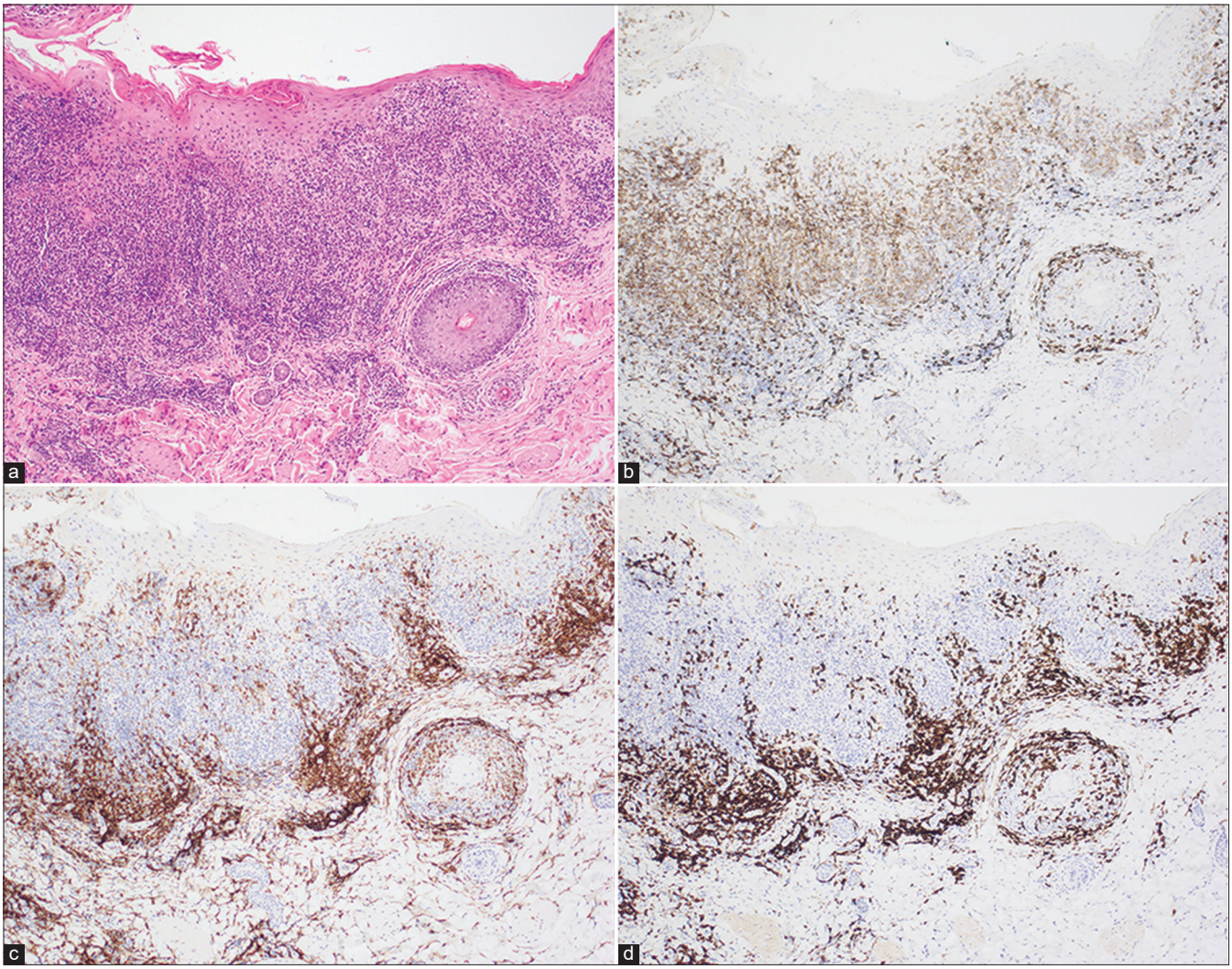

Figure 2: Histological and immunological changes identified on right thigh biopsy. (a) Prominent lichenoid lymphocytic infiltrate with widespread interface reaction (H&E x 200). (b) Positive CD8+ staining within the lower epidermis (CD8 immunohistochemistry x 100). (c) Positive CD4+ staining, concentrated at the dermoepidermal junction (CD4 immunohistochemistry x 100) (d) Positive but reduced CD5+ staining noted in the lower epidermis (CD5 immunohistochemistry x 100)

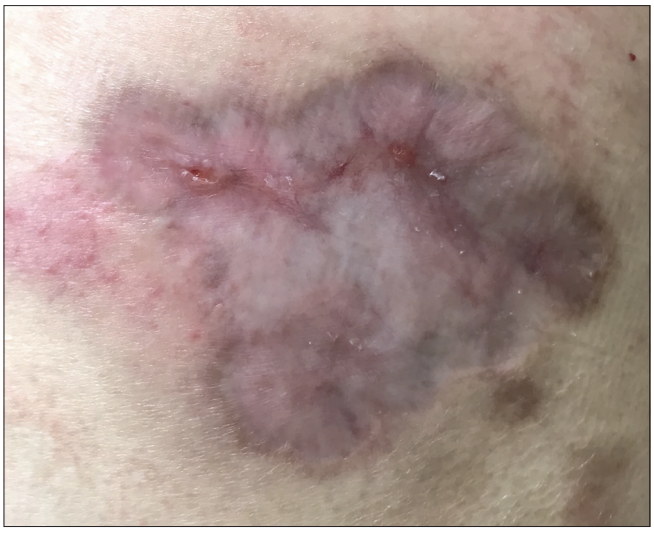

Figure 3: Healing of ulcerated plaque on right hip, three months after completing chemotherapy

that was initially misdiagnosed as pyoderma gangrenosum due to ulceration secondary to massive epidermotropism and a scarcity of atypical cells.[1] Second, the hip ulcer enlarged despite immunosuppressive therapy and rapidly responded to chemotherapy along with the other biopsy-proven cutaneous lymphoma ulcers. Finally, this lymphoma is known to follow an aggressive clinical course, where rapid tumour expansion may occur.[2] It is likely that the initial hip ulcer expansion post-debridement was due to the natural history of this aggressive lymphoma rather than true pathergy.

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma is a rare malignancy and represents less than 1% of all cutaneous T-cell lymphomas.[3] The differential diagnosis is wide and includes mycosis fungoides, pagetoid reticulosis of the Ketron-Goodman type, lymphomatoid papulosis and anaplastic large cell lymphoma.[2] Clinically, this condition presents as widespread plaques or nodules, some of which may be hyperkeratotic and rapidly undergo central necrosis.[2] Unfortunately, this type of cutaneous T-cell lymphoma follows an aggressive course with early metastasis to extranodal sites, and a poor prognosis despite chemotherapy.[2]

With regard to differential diagnoses, mycosis fungoides usually has a CD4+ immunophenotype, but can also rarely be CD8+.[2] However, it classically has an indolent course beginning with patches that may progress slowly overtime to plaques and ulcerative tumours.[2] Pagetoid reticulosis of the Ketron-Goodman type is sometimes difficult to histologically differentiate from primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma, with pagetoid epidermotropism being present, and immunophenotyping showing either CD4-/CD8- or CD4+/CD8+ cells, with tumour cells localised to the epidermis.[4] Similar to mycosis fungoides, lesions begin as hyperkeratotic patches which progress to plaques overtime, although the clinical course is more aggressive and carries a poorer prognosis.[4] Lymphomatoid papulosis can also be virtually indistinguishable from primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma on histology alone and is CD30+ and either CD4+ or CD8+.[5] Clinically, however, it presents quite differently with necrotic papules and nodules that spontaneously regress over a few months.[5] Finally, cutaneous anaplastic large cell lymphoma is CD30+, has positive staining for granzyme B and perforin and is ALK negative which is similar to primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma.[5] Differentiating features are the presence of sheets of tumour cells infiltrating the dermis, and the presence of papules or nodules rather than plaques.[5]

The diagnosis of this condition can often be challenging, especially due to a variable histological appearance.[6] It is, therefore, critical to obtain adequate tissue samples, perform appropriate immunohistochemical tests and ensure an accurate clinicopathological correlation.

Declaration of patient consent

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

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Conflicts of interest

There are no conflicts of interest.

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