QUIZ SECTION

An Ulcerated Nodule on the Toe in an Elderly Patient: A Quiz

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A 61-year-old female presented with an ulcerated prominent brown nodule present on her left toe for 3 months (Fig. 1). Physical examination revealed a 1 x 1 cm brown prominent nodule with ulceration on the left big toe and palpable lymph nodes in the left groin. She denied preceding trauma or exposure to the local site, and had no fever, malaise, or weight loss. Her medical and family histories were unremarkable. A biopsy of the toe lesion was performed for histopathological examination.

Histopathological examination revealed sheets of large, pleomorphic lymphoid cells with abundant amphophilic cytoplasm and horseshoe/kidney-shaped nuclei (Fig. 2A, B). Immunohistochemical staining results were positive for CD30 (Fig. 2C), EMA, anaplastic lymphoma kinase (ALK, Fig. 2D), CD2, LCA, and perforin, while negative for HMB45, A103, SOX10, CD20, CD79a, and EBER. A positron emission tomography (PET)-CT scan found multiple enlarged lymph nodes and nodular lesions in the left neck, clavicular and inguinal regions, posterior peritoneum, left toe, muscle space of left lower limb, and multiple sites in the bones with significant fluro-2-deoxy-D-glucose uptake. Puncture biopsy of the enlarged inguinal lymph node revealed similar histological and immunochemical features. Bone marrow aspiration and biopsy revealed no abnormalities.

What is your diagnosis?

1: Primary cutaneous anaplastic large cell lymphoma
2: ALK-positive anaplastic large cell lymphoma
3: Amelanotic melanoma
4: Lymphomatoid papulosis

See next page for answer.

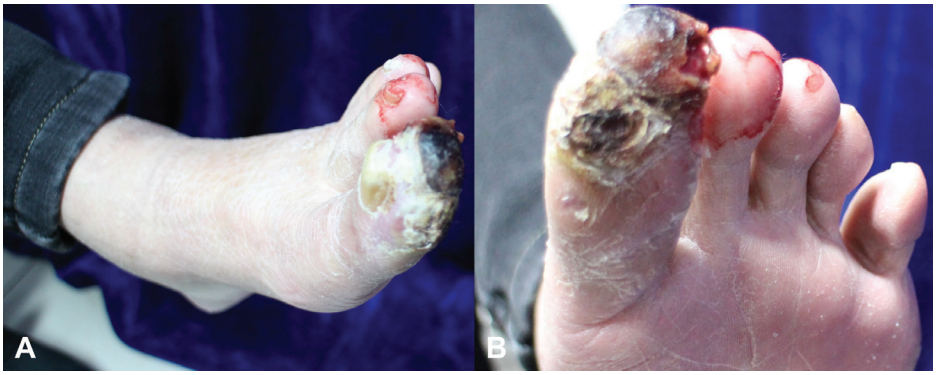

Fig. 1. An ulcerated prominent brown nodule on the toe. (A) Overview, (B) close-up view. Written patient consent for publication was obtained.

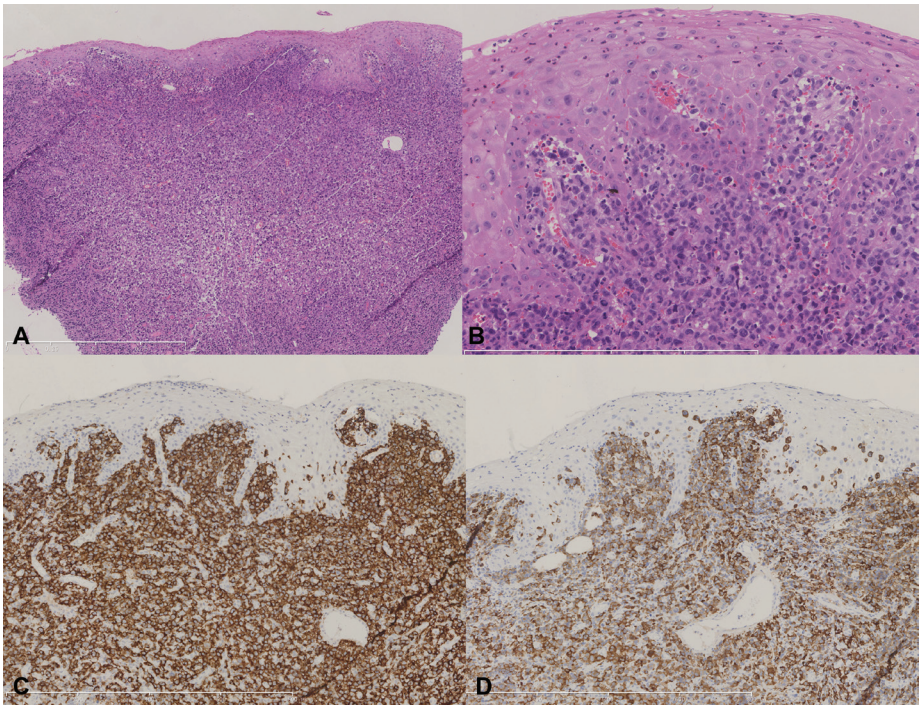

Fig. 2. Histopathological image demonstrates sheets of large, pleomorphic lymphoid cells in the dermis (A, haematoxylin eosin, x50) with abundant amphophilic cytoplasm, some of which have horseshoe/kidney-shaped nuclei (B, haematoxylin eosin, x200). Immunohistochemical staining revealed the lymphoid cells were positive for CD30 (C: CD30 x100) and ALK (D: ALK x100).

ANSWERS TO QUIZ

An Ulcerated Nodule on the Toe in an Elderly Patient: A Commentary

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***Diagnosis*: ALK-positive anaplastic large cell lymphoma**

ALK-positive anaplastic large cell lymphoma (ALK+ALCL) is a subtype of peripheral T-cell lymphoma (PTCL) histologically characterized by distinct cell morphology and expression of CD30 and ALK. ALK+ALCL usually occurs in young subjects (median age: 34 years) with a male predominance (M:F ratio: 1.5), accounting for 3% of adult non-Hodgkin lymphomas and 10–15% of childhood lymphomas (1). As it is an aggressive CD30-positive T-cell lymphoma, patients with ALK+ALCL frequently present with advanced-stage disease (stage III–IV in 66% of cases) (1). Extranodal involvement has been observed in 60% of cases, most commonly in the soft tissue and bone. According to a retrospective study including 1,306 systemic ALK+ALCL patients with extranodal involvement, 47.5% of patients had primary cutaneous/soft tissue lesions (2). Moreover, patients with primary disease presentations in the head and neck, cutaneous/soft tissue areas, and bone had a better prognosis than those located in the central nervous system and chest/abdomen/pelvis (2).

Although ALK+ALCL shows a broad morphologic spectrum, all cases contain a variable proportion of large anaplastic cells with horseshoe/kidney/embryo-shaped nuclei, referred to as hallmark cells. The common pattern exclusively consists of large-sized cells with hallmark appearance, accounting for 60% of cases (3). Other morphologic variants including lymphohistiocytic, small cell, and Hodgkin-like patterns are more difficult to diagnose as the tumour cells are mixed with reactive lymphocytes and histiocytes, and cluster around blood vessels, which might resemble a metastatic tumour. Immunostaining of CD30 and/or ALK could highlight tumour cells and aid in differential diagnosis. The majority of ALK+ALCL are positive for EMA, and expresses 1 or more T-cell antigens and cytotoxic markers (TIA1, granzyme B, perforin). Some 90% of ALK+ALCL cases show clonal rearrangement of TCR genes and harbour t(2;5) (p23;q35)/NPM-ALK translocation, which results in up-regulation of ALK (3). ALK+ALCL is consistently negative for Epstein–Barr virus.

The first clinical differential diagnosis of a progressing ulcerated erythematous nodule on the toe is amelanotic melanoma, which contains little or no pigmentation by naked eye or histologic examination. Pathologically, melanoma cells have various morphologies which could mimic carcinoma, sarcoma, and lymphoma. Notably, rare $CD30^+$ melanoma cases have been reported (4), which highlighted the importance of immunohistochemical panels including S100, SOX10, and HMB45. Skin-involved nodal ALCL needs to be differentiated from primary cutaneous $CD30^+$ T cell proliferative disorders (LPDs). Primary cutaneous $CD30^+$ LPDs are the second most common cutaneous lymphoma after mycosis fungoides and Sezary syndrome, which include primary cutaneous anaplastic large cell lymphoma (pcALCL), lymphomatoid papulosis (LyP), and borderline lesions. While LyP is characterized by disseminated self-regressing papules with a benign but recurrent clinical course, pcALCL usually manifests as a single or grouped reddish-brown plaques and nodules that sometimes ulcerate, which needs to be distinguished from secondary involvement of nodal ALK-negative ALCL based on correlation between clinical, histological, and immunophenotypical aspects.

Traditional therapy of anthracycline-based polychemotherapy CHOP (cyclophosphamide, vincristine, doxorubicin liposome, methylprednisolone) with or without etoposide is associated with an overall response rate of 90% and a 5-year overall survival of 70% in ALCL patients (5). Recently, CD30 antibody-drug conjugates (brentuximab vedotin) plus cyclophosphamide, doxorubicin, and prednisone (BV+CHP) have become the first-line treatment for systemic ALCL based on the ECHELON-2 trial data (6). Our patient, due to economic considerations, completed 6 cycles of CHOEP polychemotherapy with complete remission of the enlarged lymph nodes and skin lesion.

In summary, we present a case of ALK+ALCL manifested as an ulcerated nodule on the toe, which broadens the clinical differential diagnosis of acral tumour. More importantly, our case illustrates the importance of ALK staining in the diagnosis of CD30-positive lymphoma or lymphoproliferative disease and emphasizes the ultimate need for systemic evaluation, especially in ALK-positive cases.

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