

BRIEF ARTICLES

A Case of ALK-Negative Anaplastic Large Cell Lymphoma Presenting as a Solitary Cutaneous Nodule

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ABSTRACT

Anaplastic large cell lymphomas (ALCLs) are a group of CD30 positive T-cell non-Hodgkin lymphomas, accounting for only 3% of all non-Hodgkin lymphomas. As per the 2017 World Health Organization updated classification, there are four variants of ALCL: anaplastic lymphoma kinase (ALK) positive, ALK negative, primary cutaneous, and breast-implant associated. The different variants of ALCL share overlapping clinical presentations and pathologic features, creating a diagnostic challenge. A 71-year-old woman with a past history of T-cell lymphoma presented with a progressively growing nodule on her back for approximately 3 months. Physical exam demonstrated a 8.0 x 8.0 cm pink nodular indurated plaque located on her left upper back. A punch biopsy of the lesion revealed medium to large mononuclear cells with nuclear pleomorphism, hyperchromasia, and scattered mitotic figures. Immunohistochemistry demonstrated cells that were positive for CD30 and negative for ALK. Based on clinical and histopathologic findings, a diagnosis of ALCL was rendered. Differential diagnosis included primary cutaneous ALCL and cutaneous involvement by systemic ALK(-) ALCL. This case demonstrates the importance of clinicopathologic correlation in diagnosing ALCL and guiding therapy.

INTRODUCTION

Anaplastic large cell lymphoma (ALCL) represents a group of CD30 positive T-cell non-Hodgkin lymphomas unified by common morphologic and immunophenotypic characteristics, but with a spectrum of clinical presentations and behaviors.¹ Recognition of anaplastic lymphoma kinase (ALK) gene rearrangements in some ALCLs led to ALK being considered an important diagnostic and prognostic biomarker, and a key driver of ALCL pathobiology. As per the 2017 World Health Organization updated

classification, there are four distinct variants of ALCL: ALK-positive ALCL (ALK(+) ALCL), ALK-negative ALCL (ALK(-) ALCL), primary cutaneous ALCL (PC-ALCL), and breast-implant associated ALCL.^{1,2}

The different subtypes of ALCL share overlapping clinical presentations and pathologic features which can be diagnostically challenging.¹ Despite only accounting for 3-5% of all non-Hodgkin lymphomas, distinguishing between each ALCL subtype is important as treatment and prognoses vary.^{2,3} ALK (-) ALCL mimics ALK (+) ALCL morphologically and

immunohistochemically without the ALK gene rearrangement, making these two entities readily distinguishable. However, ALK(-) ALCL and PC-ALCL both lack the ALK gene and are more difficult to discern since there are no robust pathognomonic features to identify them.¹ ALK (-) ALCL and PC-ALCL are known to be predominant in men and typically affect patients in late adulthood with ALK(-) ALCL having a median age of presentation of 65 years versus 55 years for PC-ALCL.¹ Patients with ALK(-) ALCL usually present with “B” symptoms (fevers, night sweats, weight loss) whereas those with PC-ALCL primarily present with cutaneous nodules; however, systemic ALK(-) ALCL has been known to have extranodal involvement in the skin in 20% of cases.^{1,2,4}

Herein, we describe the case of a patient who presented with an indurated nodular plaque which, upon biopsy and

immunohistochemistry, was diagnostic of ALCL with differential diagnoses including cutaneous involvement by systemic ALK (-) ALCL and PC-ALCL.

CASE PRESENTATION

A 71-year-old woman with a remote history of T-cell lymphoma presented with a progressively growing nodule on her back for approximately 3 months. Physical exam demonstrated a 8.0 x 8.0 cm pink nodular indurated plaque located on her left upper back (Figure 1A). A punch biopsy of the lesion revealed an interstitial infiltrate within the reticular dermis (Figure 1B) composed of medium to large mononuclear cells with nuclear pleomorphism, hyperchromasia, and scattered mitotic figures (Figure 1C). The cells were shown infiltrating between collagen bundles with some having a more angiocentric distribution. No significant

Figure 1. (A) Pink nodular indurated plaque located on the left upper back. (B) Interstitial infiltrate within the reticular dermis. (C) Medium to large mononuclear cells with nuclear pleomorphism, hyperchromasia, and scattered mitotic figures.

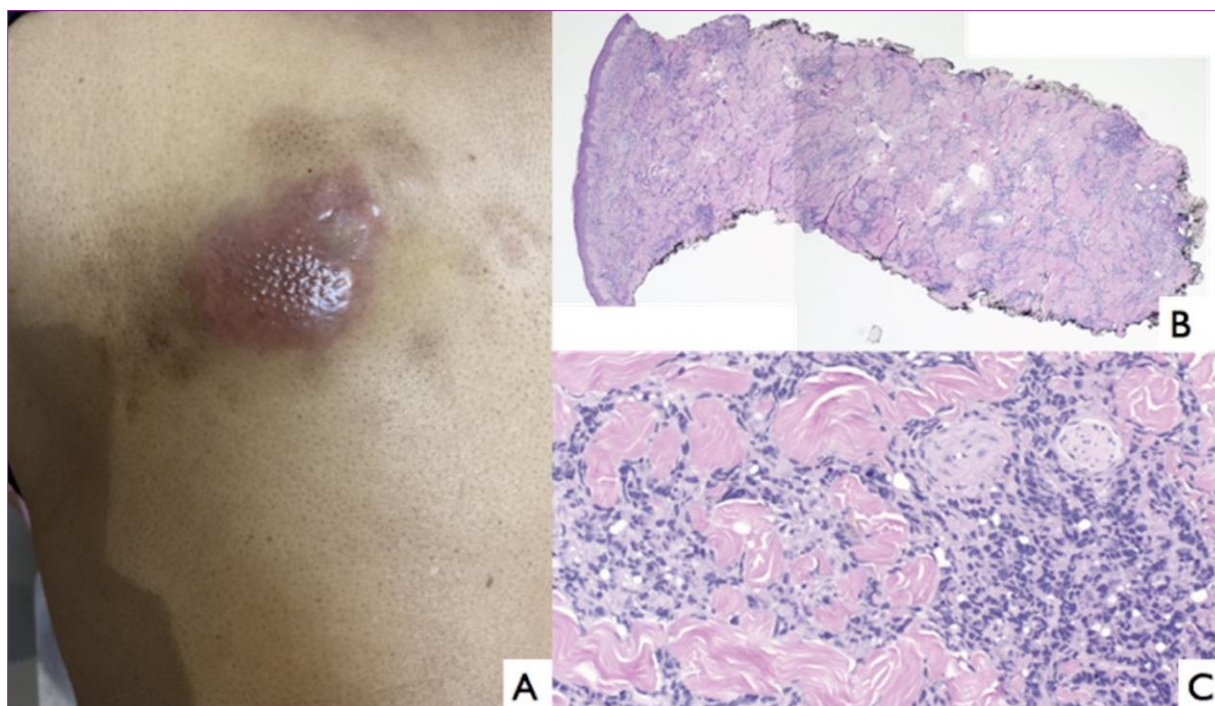
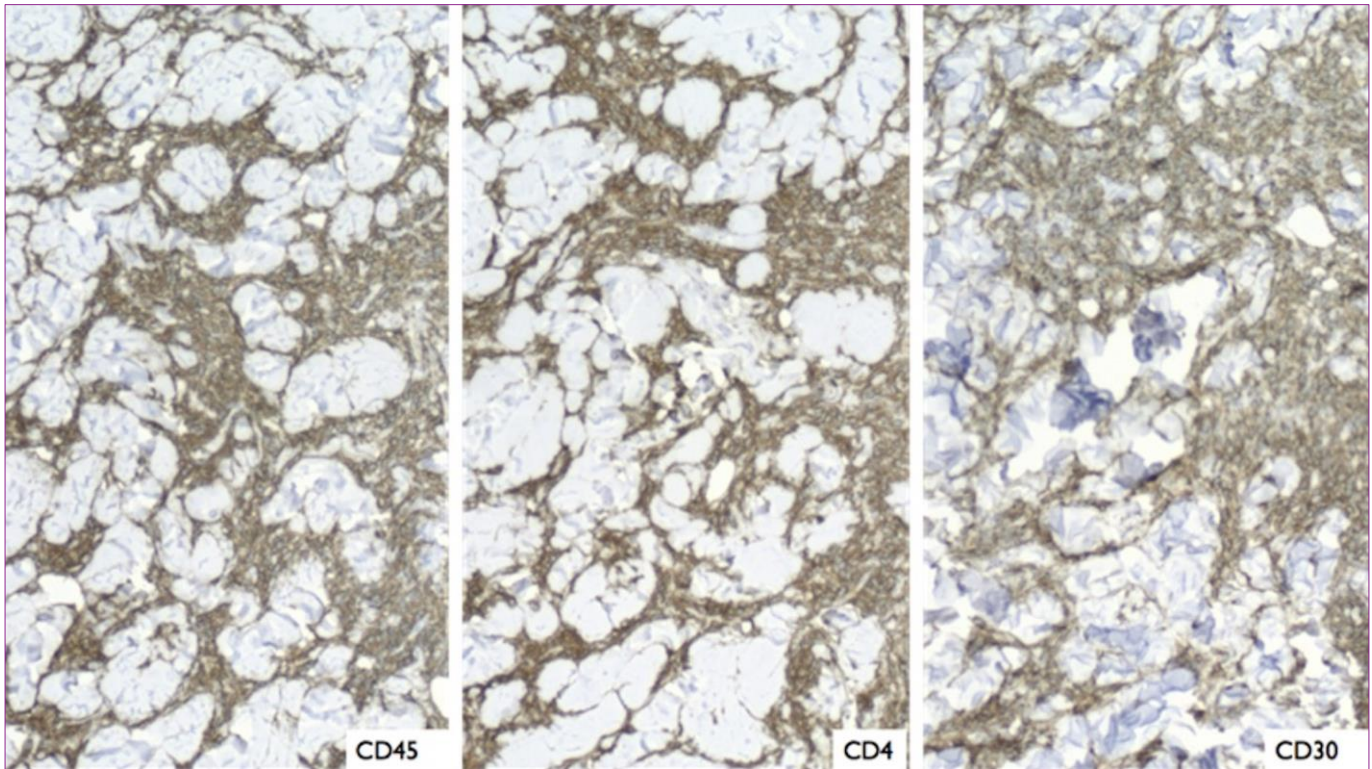


Figure 2. Immunohistochemistry demonstrating cells diffusely positive for CD45, CD4, and CD30 with areas of Golgi pattern staining.



epidermotropism was evident. Immunohistochemistry demonstrated cells that were diffusely positive for CD4, CD45, and CD30 with areas of Golgi pattern staining (Figure 2). The tumor cells were negative for CD2, CD3, CD5, CD7, CD8, CD20, CD34, CD56, CD123, TIA, granzyme, myeloperoxidase, HHV8, EBER, and ALK. A PET CT scan was performed which showed the lesion on the left upper back, but also a right breast mass and a thyroid nodule. A biopsy of the breast mass revealed an invasive ductal carcinoma. A thyroid biopsy was benign. Given the localized lesion without extracutaneous involvement, a diagnosis of PC-ALCL was rendered and the patient was scheduled for radiation therapy. After completion of radiation therapy, the patient exhibited complete resolution of the mass to her upper back without evidence of lymphadenopathy or recurrent disease.

DISCUSSION

In order to distinguish between ALK(-) ALCL and PC-ALCL, correlation with clinical and radiologic data is necessary. Our patient presented with a solitary cutaneous nodule which is primarily characteristic of PC-ALCL. ALK(-) ALCL and PC-ALCL are almost identical morphologically and immunohistologically with both strongly positive for CD30 and negative for ALK.^{1,5} Both ALK (-) ALCL and PC-ALCL have large cells with polylobulated nuclei. ALK (-) ALCL has the characteristic pathological feature of 'hallmark' cells, which resemble large cells with eccentric, kidney-shaped nuclei with a perinuclear eosinophilic Golgi region. [1]. Radiological imaging can assist in determining extracutaneous involvement and distinguishing between PC-ALCL and cutaneous involvement of systemic ALK(-)

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ALCL since PC-ALCL rarely disseminates beyond the skin.^{1,4} For our patient, a PET CT scan was critical in ruling out a cutaneous manifestation of systemic ALK(-) ALCL, especially given her remote history of T-cell lymphoma. Ideally, genetic analysis can be ordered along with a PET scan to aid the diagnostic process.

Differentiating between ALK(-) ALCL and PC-ALCL is important in determining an appropriate treatment regimen. Observational studies and randomized control trials showing an effective treatment for ALK(-) ALCL are lacking; however, a treatment regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is frequently used as first-line therapy.² Patients with ALK(-) ALCL have relapsed after CHOP therapy, and recent studies have shown treatment with Brentuximab vedotin to lead to a loss of CD30 expression.^{6,7} Treatment for PC-ALCL is dependent on whether it is a localized lesion or multifocal disease. For localized lesions, radiation therapy or surgical excision are the preferred methods of treatment.⁸ For multifocal or extracutaneous disease, short term CHOP therapy is often recommended.⁹ Recurrence of disease after treatment with CHOP regimen has been seen in both ALK(-) ALCL and PC-ALCL. Further treatment is then recommended based on radiologic and clinical correlation.

Outcomes and survival rates for both ALK(-) ALCL and PC-ALCL vary based on prescribed treatment and spread of disease. The 5-year overall survival for ALK(-) ALCL ranges from 17% to 90%, with the mean survival being 49%.¹⁰ Studies have shown CHOP regimen to treat systemic ALCL to complete remission rates of 56%.⁶ Overall prognosis for patients diagnosed with PC-ALCL, both localized and multifocal, and treated with either surgical excision or

radiation therapy is very favorable, with long term survival rates above 90%.¹¹

Our unique case does not serve as a guideline, but rather highlights the importance and inherent challenge of accurately diagnosing between the ALCL variants. While the different subtypes share overlapping clinical and pathological features, the recommended treatment regimens and prognoses are distinct. As ALCLs are a rare group of non-Hodgkin's lymphoma, large-scale clinical trials and literature remain scarce. Further research focused on identifying clear immunohistochemical markers to differentiate ALK(-) ALCL and PC-ALCL would assist physicians with diagnosis.

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