Case Report

An Unusual Presentation of ALK-Negative Anaplastic Large Cell Lymphoma: A Case Report

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Abstract

Introduction: Anaplastic large cell lymphoma (ALCL) is a rare but aggressive type of non-Hodgkin's lymphoma that develop from mature T cells. Case: A 73-year-old male presented with a swelling over the medial aspect of the right leg. An excision biopsy was performed, and histopathological examination revealed a malignant round cell neoplasm. Immunohistochemistry was negative for *CD45*, *CD20*, and *CD3* showing strong, diffuse *CD30* positivity. Based on diffuse *CD30* positivity, further immunohistochemical markers, including *ALK* and additional T-cell markers were done and a diagnosis of *ALK*-negative ALCL was made. Conclusion: ALCL can rarely present with the absence of characteristic hallmark cells and negativity for *CD45* and some of the T cell markers. *CD45* and *CD3* negativity can lead to misdiagnosis by omission of further markers. In this case, further lymphoid markers were done due to the diffuse *CD30* positivity. Hence, *ALK*-negative ALCL is a diagnostic challenge. ALCL may rarely lack characteristic hallmark cells and show negativity for *CD45* and certain T-cell markers, which can lead to diagnostic pitfalls if additional immunohistochemical workup is not performed. In the present case, diffuse *CD30* positivity prompted further lymphoid marker evaluation, leading to the correct diagnosis. This highlights that *ALK*-negative ALCL remains a diagnostic challenge and highlights the importance of a broad immunohistochemical panel in atypical presentations.

Keywords: Lymphoma; T-Cell; Large-Cell; Anaplastic

Introduction

Anaplastic large cell lymphomas (ALCLs) are a group of lymphomas originating from mature T-cells. While these lymphomas share similar characteristics in terms of their cell appearance and protein markers, they exhibit significant differences in how they present clinically, their disease progression, and their underlying genetic makeup [1]. *ALK*-negative and *ALK*-positive ALCLs show uniform diffuse *CD30* positivity [1]. Both are aggressive forms that most commonly present with lymphadenopathy, advanced-stage disease, and B symptoms. The involvement of extranodal sites is common, more in *ALK*-positive than *ALK*-negative ALCL [3].

Affecting a wide range of ages and both nodal and extranodal sites, its morphological and immunochemical characteristics often mimic those of various other cancers [2]. The lymph nodes and extranodal sites are involved in a ratio 1:1 [1]. The

extranodal sites include soft tissue, mediastinum, bone marrow, liver, spleen, gastrointestinal tract, and breast [1]. The involved tissue shows diffuse infiltration by large cells with pleomorphic lobated vesicular nuclei with prominent nucleoli. Hallmark cells (cells with eccentrically placed large horseshoe-shaped nuclei, multiple nucleoli, and abundant amphophilic cytoplasm) are commonly seen. Mitosis is brisk [1]. But the morphological spectrum is broad and need not present with the classic features.

ALK-negative ALCL has a poor prognosis, and patients are prone to relapses and refractoriness to treatment [4].

Here, we report a case of extranodal *ALK*-negative ALCL with unusual morphological and immunohistochemical characteristics.

Case Report

A 73-year-old immunocompetent male with a medical history of hypertension, coronary artery disease status post coronary artery bypass grafting (CABG), type 2 diabetes mellitus, and chronic kidney disease presented with a swelling over the right calf for three months, which had shown a sudden increase in size. The swelling was approximately 8 × 6 cm and non-tender, noted over the medial aspect of the right leg, located superficial to the underlying muscle. Imaging of the right calf revealed a well-defined lesion in the deep subcutaneous plane of the postero-medial upper leg, appearing hypoechoic on ultrasound and T1 isointense/T2 hyperintense on MRI, measuring approximately 53 × 47 × 44 mm and was reported as a benign peripheral nerve sheath tumor, possibly schwannoma or neurofibroma.

The swelling was excised. Intraoperatively, it was in the subcutaneous plane with no deep muscle infiltration.

In pathology lab a Single skin-covered soft tissue measuring 8x5x4.5 cm was received (Figure 1). Skin was unremarkable. Cut section and serial section showed a well-circumscribed, homogenous grey-white glistening neoplasm measuring 6x5x4.5cm.

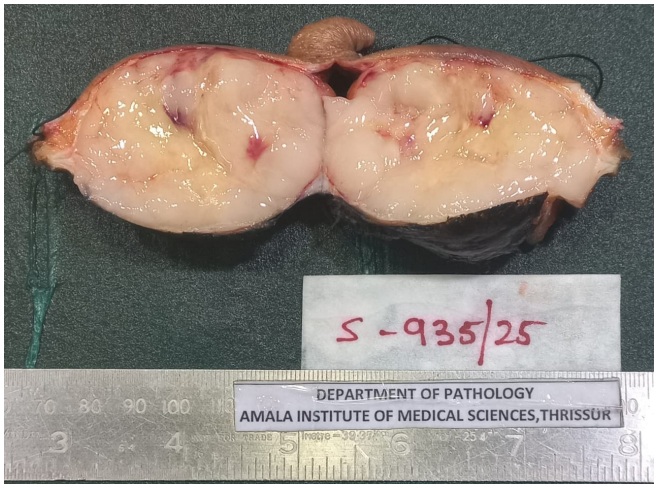

Figure 1: Gross: Well-circumscribed grey white glistening neoplasm.

Microscopy of representative areas showed a circumscribed neoplasm arranged diffusely with vague lobulations. Individual cells showed scant to moderate cytoplasm, mildly pleomorphic vesicular nucleus with prominent nucleoli, and brisk mitosis (Figure 2). Morphology favoured a malignant round cell neoplasm.

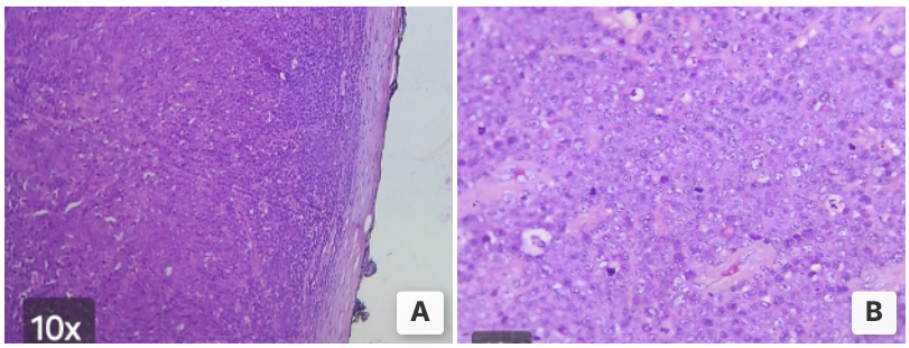

Figure 2: Shows neoplasm arranged as diffuse sheets. Individual cells have moderate cytoplasm and pleomorphic vesicular nuclei with brisk mitosis.

Immunohistochemistry was performed to further categorise the tumor.

The neoplastic cells were diffusely positive for *vimentin*, while negative for *PanCK*, *CD45*, *CD3*, *CD20*, *CD34*, *CD138*, *desmin*, *myogenin*, *MyoD1*, *synaptophysin*, *chromogranin*, and *HMB45*, thereby excluding epithelial, hematolymphoid, myogenic, neuroendocrine, and melanocytic tumors. Markers such as *TLE1*, *WT1*, *FLI1*, and *ERG* were also negative, ruling out possibilities like synovial sarcoma, peripheral nerve sheath tumors, Ewing sarcoma and vascular tumors. The *Ki-67* proliferation index was markedly elevated at 90–95%, indicating high proliferative activity. Notably, the tumor cells showed strong, diffuse positivity for *CD30*, which was pivotal in guiding the final diagnosis.

In view of the diffuse *CD30* positivity, additional immunohistochemical markers were performed to further evaluate for tumours exhibiting *CD30* expression.

Tumor cells showed diffuse positivity for *CD2* and *CD5*, with scattered positivity for *CD7*, and *granzyme B*, supporting a T-cell lineage. *CD4*-positive tumor cells were more prominent than *CD8*-positive cells. The neoplastic cells were negative for *ALK*, *TdT*, *EMA*, *CD10*, and *CD23* (Figure 3).

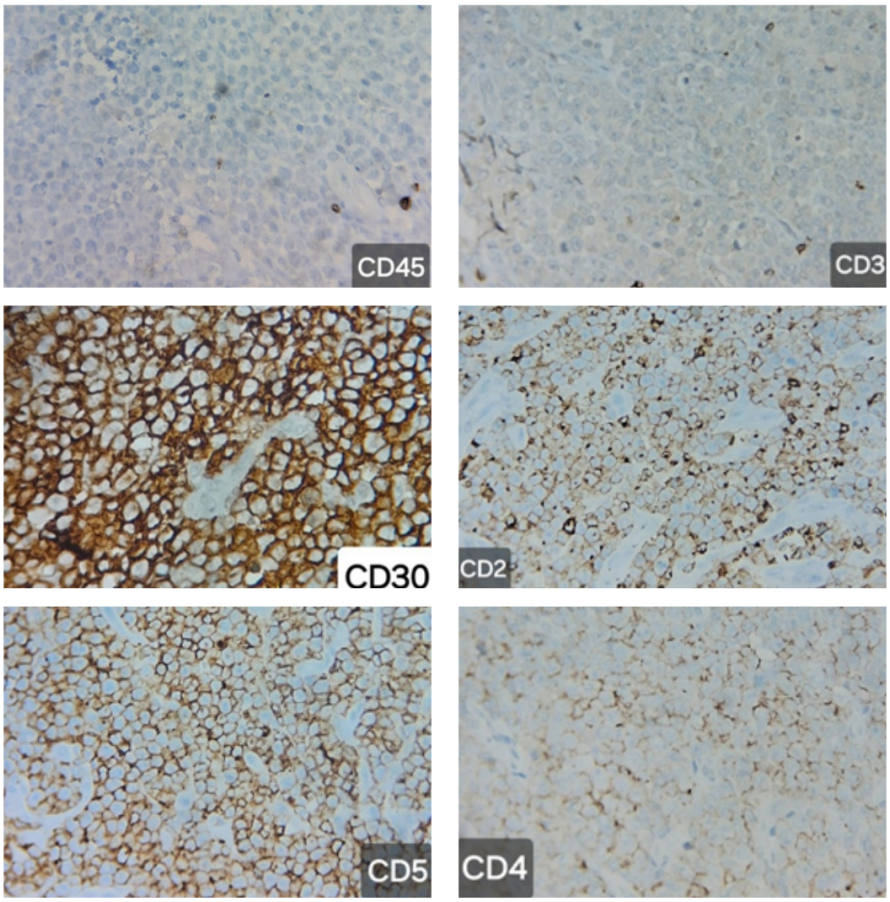

Figure 3: Immunohistochemistry showing strong and diffuse positivity for *CD30*, *CD2* and *CD5* and negative *CD45* and *CD3* (400x, scale bar-20μm).

Correlation of the immunohistochemical markers led to a final diagnosis of *ALK*-negative ALCL.

The absence of *CD45* and *CD3* expression in the tumor cells posed a significant diagnostic pitfall, as these findings initially argued against a lymphoid neoplasm. *CD45* negativity, in particular, suggested a non-hematologic malignancy, while loss of *CD3* obscured a T-cell lineage. Although the tumor demonstrated diffuse *CD30* positivity, this marker lacks lineage specificity and necessitated further immunophenotypic evaluation. Given the discordance between morphology and immunoprofile, a broad immunohistochemical panel was pursued to exclude non-hematolymphoid mimics and to identify an aberrant *CD30*-positive lymphoid neoplasm.

Discussion

Anaplastic large cell lymphoma is a rare and aggressive type of T cell lymphoma [5]. It is a mature T cell lymphoma with uniform strong expression of *CD30* with or without *ALK* expression [1].

Morphologically, classical ALCL show large lymphoid cells with abundant cytoplasm and pleomorphic horseshoe or kidney shaped nuclei which are called as hallmark cells [6].

The present case posed a diagnostic challenge to the pathologists, as these cells were absent and the initial immunohistochemistry workup showed negative *CD45*, *CD3*, and *CD20* expression in tumor cells, as these are considered lineage-defining markers. Their absence can strongly bias interpretation toward a non-hematolymphoid malignancy.

The most critical stain for diagnosing ALCL is diffuse and strong *CD30* membrane and Golgi positivity [2]. *CD45* expression may vary in ALCL.

Other *CD30* positive lymphomas include: 1) Peripheral T cell lymphoma- Not otherwise specified (PTCL NOS), and 2) Hodgkin's lymphoma.

PTCL-NOS, usually presents as lymphadenopathy and microscopy shows similar tumor cells but has variable *CD30* positivity and decreased expression of *CD5* and *CD7* [1]. In this case the cells showed uniform strong *CD30* positivity and *CD5* expression.

Hodgkin's lymphoma, show *CD15* positivity, while other T-cell markers will be negative. In ALCL, *CD2*, *CD4*, *CD5*, and *CD7* are variably positive, demonstrating a T-cell lineage and *CD15* is negative [7].

Several reports in the literature have described similar diagnostic challenges in *ALK*-negative ALCL, where strong *CD30* expression coexists with the absence of *ALK*, and variable pan-T cell marker expression. For example, a case of scalp-based *ALK*-negative ALCL has been reported where the neoplasm was composed of large pleomorphic cells with anaplastic morphology and demonstrated strong *CD30* expression but lacked *CD45*, *CD3* and *ALK* expression [8]. Another is a Brazilian case in which the tumor demonstrated classic anaplastic morphology with diffuse *CD30* expression and absence of *ALK*, *CD3* and *CD20* expression, but the site was axillary lymph node [9].

These reports collectively emphasize that *ALK*-negative ALCL may closely mimic poorly differentiated non-hematolymphoid malignancies, particularly in unusual clinical settings, and underscore the critical importance of correlating morphology with a broad immunohistochemical panel to achieve accurate and timely diagnosis.

Early recognition of *ALK*-negative anaplastic large cell lymphoma in the initial biopsy is clinically significant, as accurate classification directly influences therapeutic decisions and prognostic stratification, thereby avoiding inappropriate management [1].

Follow up: A whole-body FDG PET-CT performed one month later showed post-biopsy changes in the right calf, suggesting possible microscopic residual disease. Two months post-surgery, the patient presented with a 3 $\times$ 3 cm swelling at the same site. Revision surgery was performed, the nodule was found near the previous excision scar. The histopathology of the recurrent lesion was similar to that of the primary tumor (Figure 4). The patient is currently receiving adjuvant radiotherapy using the S-IMRT technique to a total dose of 30–36 Gy delivered in 15–20 fractions.

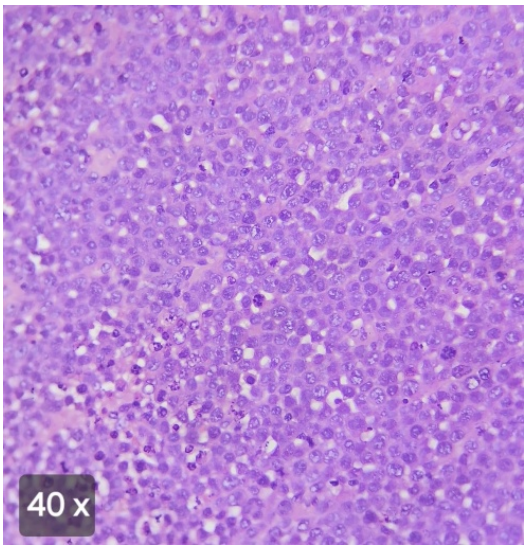

Figure 4: Re-excision biopsy showing similar tumor morphology.

Conclusion

This case underscores the importance of a comprehensive immunohistochemical workup in evaluating undifferentiated round cell tumors, particularly those arising in uncommon extranodal sites with non-specific clinical and radiological features. Despite initial findings being inconclusive, the strong and diffuse expression of *CD30* proved pivotal in reaching the diagnosis of *ALK*-negative anaplastic large cell lymphoma. This highlights the critical role of *CD30* as a diagnostic marker and its value in differentiating ALCL from other morphologically similar neoplasms, emphasizing the need to include

it routinely in the panel for soft tissue tumors of uncertain lineage. Furthermore, *CD30* positivity should also trigger an extensive T cell marker workup.

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Competing Interests: The authors declare that they have no competing interests.

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