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Review Article

Systemic Alk-Positive Anaplastic Large Cell Lymphoma: A Comprehensive Pathological and Immunophenotypic Review

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Abstract: Systemic ALK-positive anaplastic large cell lymphoma (ALK+ ALCL) is a distinct entity within the spectrum of peripheral T-cell lymphomas. Although relatively uncommon, its diagnosis in clinical practice remains challenging due to its broad histological diversity. The presence of multiple morphological variants frequently leads to diagnostic pitfalls, including misinterpretation or underdiagnosis when relying solely on routine Hematoxylin and Eosin (H&E) stained sections. Immunohistochemistry plays a critical role in establishing a definitive diagnosis; however, access to comprehensive antibody panels remains limited in many resource-constrained settings. This review provides a comprehensive synthesis of the diverse morphological variants and immunophenotypic profiles of ALK+ ALCL. By consolidating current knowledge on histopathological features and essential immunohistochemical markers, this work serves as a detailed reference to support the accurate identification and better understanding of this complex entity in clinical practice.

Keywords: ALK-Positive ALCL, Non-Hodgkin Lymphoma, Peripheral T-cell Lymphoma, Histopathology, Morphological Variants, Immunohistochemistry, CD30, ALK Protein.

1. INTRODUCTION

According to GLOBOCAN 2022 statistics, there were nearly 20 million new cancer cases worldwide, with approximately 9.7 million cancer-related deaths. Among these, non-Hodgkin lymphoma accounted for 2.8% of new cases and 2.6% of deaths, ranking 10th in incidence and 11th in mortality across all 36 common cancer types (Bray F *et al*., 2024).

ALK+ ALCL is a rare entity within the category of mature T-cell non-Hodgkin lymphomas. It is characterized by CD30 positivity and aberrant anaplastic lymphoma kinase (ALK) protein expression resulting from genetic mutations involving ALK gene rearrangements (Elenitoba-Johnson KS *et al*., 2024).

As recorded in the 5th edition of the World Health Organization (WHO) Classification of Tumours, ALK+ ALCL accounts for approximately 3% of adult non-Hodgkin lymphomas (Elenitoba-Johnson KS *et al*., 2024). In the pediatric population, ALK+ ALCL comprises 15% of all non-Hodgkin lymphoma cases, with a global incidence of 1.2 cases per million children (Lamant-Rochaix L, 2024).

Despite its distinct molecular signatures, the clinical diagnosis of ALK+ ALCL is frequently complicated by its remarkable morphological diversity, which can mimic various other malignancies. This often leads to diagnostic pitfalls, especially in settings with limited access to extensive immunohistochemical markers. Therefore, the purpose of this review is to provide a comprehensive synthesis of the various morphological variants and immunophenotypic profiles of ALK+ ALCL. By consolidating updated diagnostic criteria and histopathological features, this work aims to offer a detailed reference to enhance diagnostic precision and support better management of this complex lymphoma in clinical practice.

2. RESEARCH METHODS

This study employed a narrative review approach to synthesize current evidence related to the histopathological and immunophenotypic profiles of systemic ALK+ ALCL.

A literature search was conducted using electronic databases including PubMed, Scopus, and Google Scholar. The search focused on high-quality peer-reviewed studies, the 5th edition of the WHO Classification of Tumours, and the latest National Comprehensive Cancer Network (NCCN) guidelines to ensure the inclusion of updated diagnostic criteria.

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Articles were selected based on the following inclusion criteria:

- Studies detailing the morphological spectrum and variants of ALK+ ALCL.
- Research addressing the diagnostic role of immunohistochemical markers (CD30, ALK, EMA, and T-cell antigens).
- Recent updates on the prognostic and therapeutic implications of specific immunophenotypes.

Note on Image Originality:

All photomicrographs (Figures 1–5) presented in this review are original images captured directly by the author from clinical diagnostic practice. No images were reproduced or extracted from external published sources.

3. RESULTS AND DISCUSSION

3.1 Clinical Features and Anatomic Distribution

ALK+ ALCL typically presents as an acute, rapidly progressive systemic disease. A hallmark of its clinical presentation is the high frequency of advanced-stage disease (Ann Arbor stage III–IV) and the prominence of constitutional B-symptoms, which are observed in approximately 75% of patients (Elenitoba-Johnson KS *et al*., 2024).

The anatomic distribution of ALK+ ALCL is notably diverse, involving both nodal and extranodal sites. Peripheral, mediastinal, or abdominal lymphadenopathy is present in nearly 90% of cases and extranodal involvement is frequent (60%) with skin (26%), bone (14%), soft tissue (15%) and lung (14%) being common. The bone marrow is involved in 10-14% of patients by morphological examination alone but the frequency is higher with the use of immunostaining. Central nervous system involvement is rare at diagnosis (Medeiros LJ, 2021).

3.2 Morphological Variants

ALK+ ALCL exhibits remarkable histological diversity. A defining feature present in all cases is the presence of "hallmark cells", which are characterized by eccentric, "kidney or horseshoe" shaped nuclei and abundant eosinophilic or amphophilic cytoplasm. While hallmark cells are typically large, smaller neoplastic cells sharing similar nuclear features are also diagnostically significant. Additionally, some cells may contain eosinophilic cytoplasmic inclusions, creating a "doughnut" or "ring" cells appearance.

The morphological spectrum of ALK+ ALCL is broad, ranging from small cell proliferations to cases dominated by pleomorphic, giant cells. Based on the 5th edition of the WHO Classification, ALK+ ALCL is categorized into several histological variants as described below:

3.2.1 Common (Classic) Variant:

The common variant is the most prevalent morphological subtype, representing approximately 60% to 70% of all systemic ALK+ ALCL cases (Elenitoba-Johnson KS *et al*., 2024). This variant is characterized by a broad spectrum of cell sizes, but it is typically dominated by large pleomorphic cells. A defining cytological feature is the "hallmark cell" which contains an eccentric, kidney-shaped or horseshoe-shaped nucleus and a prominent eosinophilic region near the nucleus, representing the Golgi apparatus (Stein H *et al*., 2000), as illustrated in Figure 1.

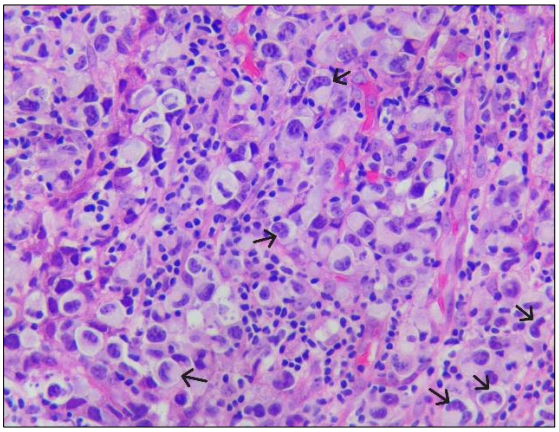

Figure 1: ALK+ ALCL, common variant, showing pleomorphic large cells and characteristic hallmark cells (black arrows) (H&E, ×400)

3.2.2 Lymphohistiocytic Variant

This variant accounts for approximately 10% of cases and is characterized by a dense infiltrate of reactive histiocytes that can obscure the neoplastic lymphoid cells. The malignant cells are often smaller than those in the common variant and frequently cluster around blood vessels (Medeiros LJ, 2021). Due to the abundance of histiocytes, this subtype may be mistaken for reactive processes or hemophagocytic syndromes. Identification of hallmark cells and the use of ALK and/or CD30 immunohistochemistry are crucial for an accurate diagnosis (Sibon D *et al*., 2012), as illustrated in Figure 2.

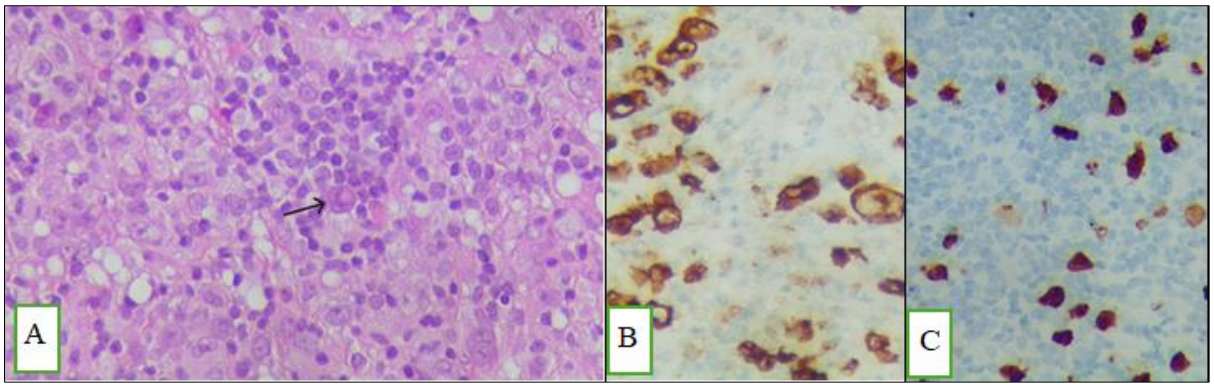

Figure 2: ALK+ ALCL, lymphohistiocytic variant

(A) Pleomorphic lesion rich in histiocytes and plasma cells, featuring large abnormal hallmark cells (black arrows) (H&E, ×400). (B) Lymphoma cells showing strong positivity for CD30 (CD30, ×400). (C) Tumor cells exhibiting both cytoplasmic and nuclear staining for ALK (ALK, ×400)

3.2.3 Small Cell Variant

The small cell variant (5-10% of cases) presents a predominant population of small-to-medium-sized neoplastic cells with irregular, indented nuclei (Elenitoba-Johnson KS *et al*., 2024). Although hallmark cells are always present, they are often sparse and tend to be distributed around high endothelial venules. This variant is clinically significant as it is frequently associated with a leukemic phase and a more aggressive clinical course (Ferreri A *et al*., 2012). It is often misdiagnosed as other T-cell lymphomas unless CD30 and ALK stains are performed, as shown in Figure 3.

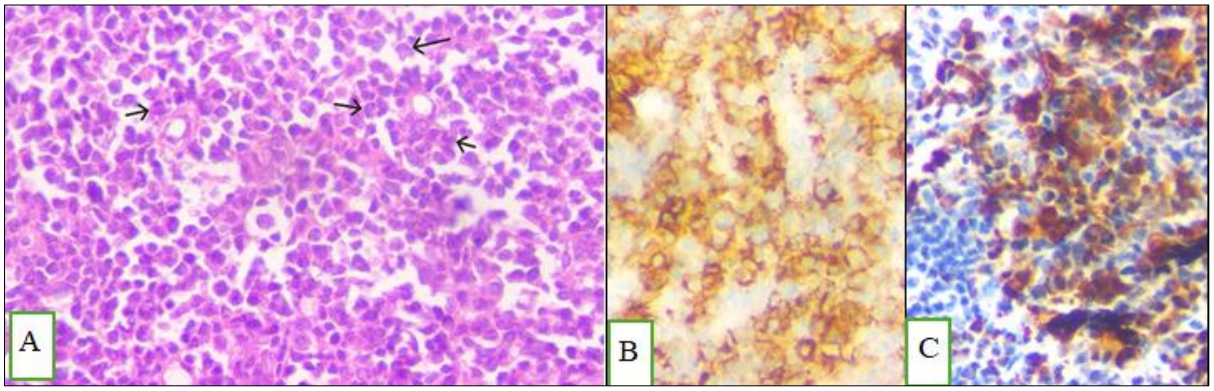

Figure 3: ALK+ ALCL, Small cell variant

(A) The lesion comprises small to medium sized lymphoma cells with irregular, kidney shaped nuclei and scant cytoplasm (black arrows); tumor cells tend to aggregate in perivascular regions (H&E, ×400). (B) Lymphoma cells showing positivity for CD30 (CD30, ×400). (C) Tumor cells exhibiting both cytoplasmic and nuclear staining for ALK (ALK, ×400)

3.2.4 Rare Morphological Patterns

Aside from the variants previously mentioned, ALK+ ALCL can manifest in several rare morphological patterns, posing significant diagnostic challenges. The Hodgkin's-pattern mimics the architectural features of nodular sclerosis classical Hodgkin lymphoma, often exhibiting a nodular growth pattern containing Reed-Sternberg-like cells (Stein H *et al*., 2000). Another uncommon presentation is the neutrophil-rich background, where a dense inflammatory infiltrate of neutrophils may predominate, potentially leading to a misdiagnosis of a pyogenic infection or an acute inflammatory process. Additionally, a sarcomatoid appearance may occur, characterized by spindle-shaped neoplastic cells resembling a soft tissue sarcoma, particularly when involving extranodal sites (Medeiros LJ, 2021), as shown in Figure 4.

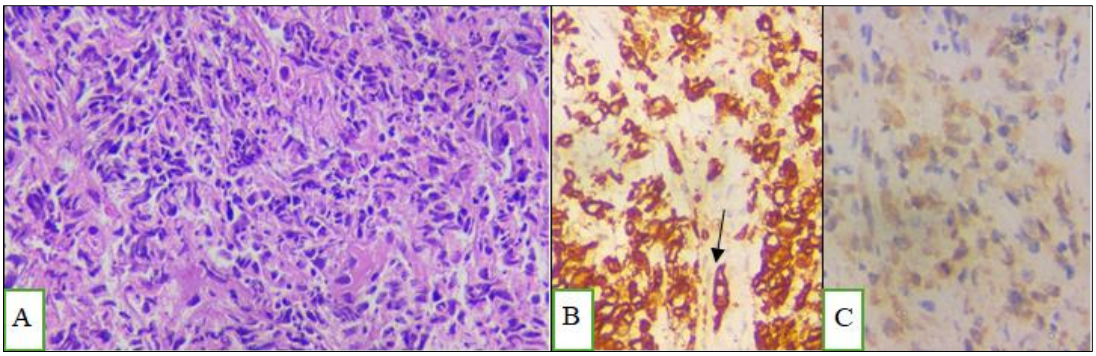

Figure 4: ALK+ ALCL with sarcomatoid appearance

A. The lesion exhibits a hypercellular proliferation of atypical spindle-shaped neoplastic cells mimicking a high-grade spindle cell sarcoma. (B) Atypical spindle-shaped neoplastic cells showing positivity for CD30 (black arrow) (CD30 stains, ×400) and (C) exhibiting cytoplasmic staining for ALK (ALK, ×400)

Due to its wide morphological spectrum, ranging from common to rare architectural patterns, ALK+ ALCL remains a diagnostic challenge. While variants exhibit unique cellular features, the presence of hallmark cells serves as a consistent diagnostic anchor across the spectrum. The following table (Table 1) synthesizes the essential histopathologic characteristics of these subtypes to facilitate a clearer comparative understanding.

Table 1: Summary of Morphological Variants and Patterns of Systemic ALK+ ALCL

Variant/pattern	Frequency (%)	Characteristic features
Common (Classic) variant	60-70%	Pleomorphic large cells, frequent "hallmark" cells.
Small Cell variant	5-10%	Small-to-medium cells, irregular nuclei, sparse hallmark cells frequently exhibit a perivascular distribution and show strong positivity for both CD30 and ALK
Lymphohistiocytic variant	10%	Abundant reactive histiocytes masking neoplastic cells. Tumor cells frequently exhibit a perivascular distribution and show strong positivity for both CD30 and ALK
Hodgkin's-like pattern	Rare	Reed-Sternberg-like cells; mixed inflammatory background. Mimics Nodular Sclerosis Classical Hodgkin Lymphoma.
Neutrophil-rich pattern	Rare	Intense neutrophilic infiltrate; potentially necrotic.
Sarcomatoid pattern	Rare	Spindle-shaped neoplastic cells; may have myxoid stroma.

3.3 Immunophenotypic Profile:

The history of ALCL is closely linked to the discovery of the CD30 antigen. In 1982, the monoclonal antibody Ki-1—later identified as CD30—was first described in Reed–Sternberg cells of Hodgkin lymphoma. Shortly thereafter, in 1985, Stein H *et al.*, recognized a distinct group of large cell lymphomas characterized by strong Ki-1 (CD30) expression and anaplastic morphology, initially termed "Ki-1–positive large cell lymphoma" (Stein H *et al*., 1985). These findings established CD30 as a defining immunophenotypic marker and laid the foundation for the recognition of ALCL as a separate clinicopathological entity. Subsequent advances in immunohistochemistry and molecular genetics, including the identification of ALK rearrangements, further refined the classification of CD30-positive lymphomas, particularly distinguishing ALK+ ALCL as a unique subtype (Bonzheim I *et al.,* 2015).

According to the 2024 NCCN guidelines for T-cell lymphomas (NCCN, 2024), the recommended immunohistochemical workup varies depending on the morphologic pattern and anatomic site of disease. In cases with anaplastic morphology, a broad panel including CD30, ALK, PAX5, CD15, EBER, cytotoxic markers (granzyme B, perforin, TIA-1), CD25, and IRF4/MUM1 is suggested to support diagnosis and exclude mimickers. For T-cell lymphomas without anaplastic features, the immunophenotypic panel is further tailored according to nodal or extranodal involvement, incorporating a wider range of T-cell and follicular helper T-cell–associated markers.

Despite this variability in diagnostic algorithms, the co-expression of CD30 and ALK remains the defining immunophenotypic hallmark of Systemic ALK+ ALCL and forms the cornerstone of its identification.

3.3.1 CD30

CD30 is uniformly and strongly expressed in virtually all cases ALK+ ALCL, representing a hallmark feature of this entity. Immunohistochemically, CD30

typically demonstrates a membranous and perinuclear Golgi staining pattern, reflecting its localization within activated lymphoid cells (Tsuyama N *et al*., 2017), as illustrated in Figure 2B, 3B and 4B.

Despite its diagnostic significance, CD30 expression is not entirely specific, as it can also be observed in other lymphoid malignancies, particularly Hodgkin Lymphoma and a subset of Diffuse Large B-Cell Lymphoma. However, in contrast to these entities, CD30 expression in ALK+ ALCL is typically diffuse and uniformly strong across the tumor cell population, providing an important diagnostic clue when interpreted in conjunction with ALK positivity (Falini B *et al*., 1999)

3.3.2 ALK

In addition to CD30, ALK protein expression represents the second defining immunophenotypic hallmark of ALK+ ALCL. Normally, ALK is expressed only in certain cells of the nervous system and is not expressed in lymphoid cells (Naoe T *et al.,* 2006). Therefore, overexpression of ALK in lymphoid lineage cells is abnormal and is considered evidence of lymphomatous pathology (Medeiros LJ, 2021).

ALK+ ALCL is defined by chromosomal rearrangements involving the ALK gene on chromosome 2p23, leading to constitutive ALK overexpression. From a pathogenetic perspective, ALK activation is central to tumor development, as pharmacologic inhibition of ALK effectively suppresses tumor growth. Although alternative ALK fusion partners are not considered primary oncogenic drivers, they play a critical role in modulating ALK expression levels and subcellular localization (Stein H *et al*., 2000). To date, 13 distinct variants of genetic alterations involving the ALK gene have been identified, as summarized in Table 2.

Table 2: Chromosomal rearrangements, partner gene and pattern of ALK expression found in ALK+ ALCL. (adapted from Elenitoba-Johnson KS *et al*., 2024)

Chromosomal abnormality	*ALK* partner	ALK staining pattern	% of cases
t(2;5)(p23;q35)	*NPM1*	Nuclear and cytoplasmic	84%
t(1;2)(q25;p23)	*TPM3*	Strong cytoplasmic and membranous	13%
Inv(2)(p23q53)	*ATIC*	Diffuse cytoplasmic	1%
t(2;3)(p23;q21)	*TFG Xlong* *TFG long* *TFG short*	Diffuse cytoplasmic Diffuse cytoplasmic Diffuse cytoplasmic	<1%
t(2;17)(p23;q23)	*CLTC*	Granular cytoplasmic	<1%
t(2;X)(p23;q11.12)	*MSN*	Membranous	<1%
t(2;19)(p23;p13.1)	*TPM4*	Diffuse cytoplasmic	<1%
t(2;22)(p23;q11.2)	*MYH9*	Diffuse cytoplasmic	<1%
t(2;9)(p23;q33-34)	*TRAF1*	Diffuse cytoplasmic	<1%
t(2;11)(2p23;11q12.3)	*EEF1G*	Diffuse cytoplasmic	<1%
t(2;17)(p23;q25)	*RNF213/ALO17*	Diffuse cytoplasmic	<1%

Notably, distinct ALK fusion partners are associated with characteristic subcellular staining patterns reflecting the intracellular localization properties of the respective partner proteins. The *NPM::ALK* fusion demonstrates both nuclear and cytoplasmic staining due to the nuclear shuttling capability of *NPM* (Figure 5A). In contrast, the *TPM3::ALK* fusion typically shows combined cytoplasmic and membranous staining (Figure 5B), whereas the *MSN::ALK* fusion is featured mainly by membranous localization. The remaining ALK rearrangements generally exhibit diffuse cytoplasmic expression (Figure 5C), with the *CLTC::ALK* variant displaying a distinctive granular cytoplasmic staining pattern.

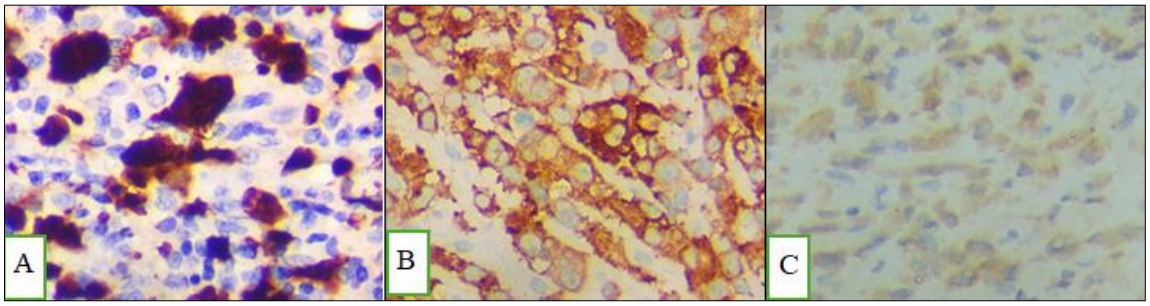

Figure 5: Immunohistochemical patterns of ALK+ ALCL, demonstrating nuclear and cytoplasmic staining (5A), strong cytoplasmic and membranous staining (5B), and diffuse cytoplasmic staining (5C).

These differences in intracellular distribution are reflected in the immunohistochemical staining patterns of ALK and have important diagnostic implications. Recognition of these staining patterns not only facilitates accurate classification of ALK+ ALCL but may also provide indirect insight into the underlying molecular subtype, thereby contributing to a more refined pathological assessment.

3.3.3 Pan-T-Cell Markers

Following assessment of the diagnostic hallmark markers CD30 and ALK, evaluation of lineage-specific antigens is essential for further characterization of the neoplastic population. Although ALK+ ALCL is classified as a T-cell lymphoma, it typically demonstrates a markedly aberrant T-cell immunophenotype.

Expression of pan–T-cell markers is frequently diminished or lost. CD3 is negative by immunohistochemistry in the majority of cases (>75%), often showing only weak or cytoplasmic staining when present. Other pan–T-cell antigens, including CD5 and CD7, are commonly downregulated or absent. In contrast, CD2 and CD4 are more frequently retained, being expressed in approximately 60–80% of cases (Swerdlow *et al*., 2017; Stein H *et al*., 2000). CD43, another T-cell–associated marker, is also commonly preserved and may be detected in up to 80–90% of cases, providing additional support for T-cell lineage in diagnostically challenging settings.

CD4 expression predominates (approximately 70–80%), supporting a helper T-cell origin, whereas CD8 expression is uncommon and typically mutually exclusive with CD4. However, certain morphologic variants, particularly the small cell variant, more often exhibit CD8 positivity or a double-negative (CD4−/CD8−) phenotype (Ferreri *et al*., 2012).

The frequent loss of multiple T-cell markers reflects the biologic plasticity of ALK-driven neoplastic transformation and contributes to significant diagnostic difficulty, particularly in cases with anaplastic morphology or limited tissue samples. In such settings, ALK+ ALCL may be misinterpreted as a non–T-cell malignancy, including poorly differentiated carcinoma or other high-grade hematolymphoid neoplasms, especially when evaluation is based on morphology alone or an incomplete immunohistochemical panel (Benharroch *et al*., 1998).

Despite this aberrant phenotype, the T-cell origin of ALK+ ALCL is supported by clonal T-cell receptor gene rearrangements in most cases, confirming its classification within the T-cell lymphoma spectrum. Therefore, recognition of this characteristic “null” or aberrant T-cell immunoprofile, in conjunction with strong CD30 and ALK expression, is essential for accurate diagnosis and appropriate classification (Swerdlow *et al*., 2017).

3.3.4 Pan–B-Cell Markers

Evaluation of pan–B-cell markers is an essential step in the immunophenotypic characterization of ALK+ ALCL, primarily to exclude B-cell lymphomas in the differential diagnosis. Tumor cells in ALK+ ALCL are characteristically negative for B-cell–associated antigens, including CD20, CD79a, and PAX5, which supports their T-cell lineage and helps distinguish them from CD30-positive B-cell lymphomas such as Diffuse large B-cell lymphoma and Hodgkin lymphoma (Stein H *et al*., 2000).

3.3.5 Epithelial Membrane Antigen (EMA)

EMA is also known as MUC1, is a high–molecular-weight transmembrane glycoprotein typically expressed on the apical surface of glandular epithelial cells. Despite its epithelial origin, EMA is frequently expressed in ALK+ ALCL, where it serves as a valuable adjunct in immunophenotypic diagnosis (Stein H *et al*., 2000). EMA expression, particularly when assessed using the monoclonal antibody clone E29, has been consistently reported to be high, with positivity rates of 87.8% (Khanlari M *et al*., 2022) and 88.2% (ten Berge RL, 2001).

Several monoclonal antibody clones against EMA have been described, including E29, 139H2, DF3, VU-4H5, and SM3. Among these, the E29 clone is widely recommended and considered particularly suitable for inclusion in immunohistochemical panels used in the diagnostic evaluation of CD30-positive large cell lymphomas (ten Berge RL, 2001).

3.3.6 CD45 (Leukocyte Common Antigen, LCA)

In the context of ALK+ ALCL, CD45 (encoded by the PTPRC gene) serves as a critical marker for identifying the hematologic origin of the neoplastic cells. However, recent evidence suggests that CD45 is not merely a passive surface marker but a functional player in the oncogenic signaling landscape of the disease.

Most cases of ALK+ ALCL demonstrate positive expression of CD45. Flow cytometric analysis reveals that the neoplastic cells are typically CD45 bright. A distinct diagnostic feature of ALCL cells is their localization on the CD45 vs. Side Scatter (SSC) plot; due to their large size and high cytoplasmic complexity, these cells often fall within the "monocyte gate" rather than the typical lymphocyte gate. This unique positioning is a vital consideration for hematopathologists to avoid false-negative interpretations during flow cytometric screening (Muzzafar T *et al*., 2009).

While CD45 is expressed, its levels are dynamically regulated by the primary oncogenic driver. The fusion protein NPM-ALK activates STAT3, which subsequently binds directly to the promoter region of the

PTPRC gene, suppressing the transcription of CD45—particularly the CD45RO isoform. This suppression is reversible; treatment with ALK tyrosine kinase inhibitors (TKIs), such as Crizotinib, or ALK-degrading PROTACs, results in a significant restoration of CD45 expression. Therefore, The expression levels of CD45 have direct implications for therapeutic outcomes. A further reduction or loss of CD45 has been linked to increased resistance to ALK inhibitors. Experimental models using CRISPR/Cas9 to knockout CD45 have demonstrated that the absence of this phosphatase renders ALCL cells less sensitive to TKI-induced apoptosis, suggesting that CD45 status may serve as a potential biomarker for predicting the efficacy of ALK-targeted therapies (Mura G *et al*., 2023).

4. Differential Diagnosis

Due to its significant morphological diversity, ALK+ ALCL must be distinguished from several benign and malignant entities to ensure appropriate clinical management (Elenitoba-Johnson KS *et al*., 2024).

- Classic Hodgkin Lymphoma (cHL): This is the most common diagnostic pitfall, especially the nodular sclerosis subtype. While both express CD30, cHL is typically ALK-negative and shows a characteristic "pauci-cellular" background with Reed-Sternberg cells. Immunophenotypically, cHL is usually PAX5+ (weak), CD15+, and negative for T-cell markers and EMA (Elenitoba-Johnson KS *et al*., 2024; Khoury JD *et al*., 2022)
- ALK-negative ALCL: Morphologically identical to the common variant of ALK+ ALCL but lacks ALK protein expression. This distinction is crucial as ALK-negative cases generally have a poorer prognosis and often harbor different genetic rearrangements, such as DUSP22 or TP63 (Parrilla Castellar ER *et al*., 2014).
- Peripheral T-cell Lymphoma, Not Otherwise Specified (PTCL, NOS): Although some PTCL, NOS cases express CD30, the expression is typically heterogeneous and weaker than the strong, uniform membrane and Golgi pattern seen in ALCL (Tsuyama N *et al*., 2017). PTCL, NOS is ALK-negative and often retains a more complex T-cell immunophenotype compared to the "null" profile of ALCL (Elenitoba-Johnson KS *et al*., 2024).
- Reactive Lymphadenopathies: The lymphohistiocytic variant of ALCL can mimic reactive processes or sinus histiocytosis. The presence of "hallmark cells" and the strong, diffuse expression of ALK and CD30 are definitive for malignancy (Khanlari M *et al*., 2022).

5. CONCLUSION

Systemic ALK+ ALCL is a distinct clinicopathological entity characterized by a remarkable spectrum of morphological variants that can mimic both reactive processes and other aggressive lymphomas. This review emphasizes that while morphology—particularly the identification of "hallmark cells"—remains the diagnostic anchor, it must be supported by a robust immunohistochemical panel (Stein H *et al*., 2000; Medeiros LJ, 2021). The co-expression of CD30 and ALK remains the gold standard for diagnosis (Falini B *et al*., 1999; NCCN, 2024).

Furthermore, understanding the aberrant "null" T-cell immunoprofile and the functional role of markers like CD45 and EMA is essential for avoiding diagnostic pitfalls and providing prognostic insights (Khanlari M *et al*., 2022; Mura G *et al*., 2023). As therapeutic strategies evolve toward targeted ALK inhibitors and immunotherapies, the pathologist's ability to accurately identify these diverse histopathological and immunophenotypic profiles is fundamental to optimizing patient management and clinical outcomes.

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