Anaplastic Large Cell Lymphoma

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Abstract

Session 8 of the 2005 Society of Hematopathology/European Association for Haematopathology Workshop was devoted to anaplastic large cell lymphoma (ALCL). Most cases submitted were anaplastic lymphoma kinase (ALK)+ ALCL highlighting unusual clinical settings, histologic variants, and variant translocation partners. Cases submitted as ALK– ALCL emphasized the immunohistochemical overlap with classical Hodgkin lymphoma (eg, CD15+/CD30+). It was also clear that consensus histologic and immunohistochemical criteria for the diagnosis of ALK– ALCL are lacking. Many expressed the opinion that ALK– ALCL is not a distinct entity at the immunophenotypic or genetic level and is better designated as peripheral T-cell lymphoma (PTCL), unspecified. Others suggested that the histologic features of ALK– ALCL are distinctive nevertheless and that this diagnosis has meaning that is lost by designating these neoplasms as PTCL, unspecified. This session also included CD30+ anaplastic lymphomas involving skin in which the differential diagnosis included cutaneous ALCL and systemic ALK– ALCL.

Historic Overview

How Has the Diagnosis of Anaplastic Large Cell Lymphoma Evolved?

Anaplastic large cell lymphoma (ALCL) has undergone extensive modification of its definition during its approximately 20-year existence. In 1985, Stein and colleagues[1] identified a subset of non-Hodgkin lymphomas characterized by anaplastic large lymphoid cells that expressed CD30, had a tendency to grow cohesively, and also had a predilection for invading lymph node sinuses. They originally named this neoplasm Ki-1 lymphoma, but the name was subsequently changed to anaplastic large cell lymphoma, its current designation in the World Health Organization (WHO) classification of lymphoid neoplasms.[2] In the original 1985 study, approximately 75% of cases were of T-cell lineage, 15% were of B-cell lineage, and 7% were of null-cell lineage.[1] A subset of cases occurred in patients with a history or simultaneous evidence of classical Hodgkin lymphoma. The authors recognized at the time that Ki-1 lymphoma as described in this initial publication was not a homogeneous entity.

Since 1985, extensive immunophenotypic and molecular studies have refined the diagnosis of ALCL. As a result, CD30+ anaplastic large B-cell lymphoma has been excluded from the ALCL category and is now grouped with diffuse large B-cell lymphoma (DLBCL). With the advent of many antibodies reactive in routinely processed tissue specimens (eg, anaplastic lymphoma kinase [ALK]-1 and PAX5/BSAP), current immunohistochemical panels can reliably distinguish between classical Hodgkin lymphoma and ALCL in most cases.[2-5] These studies also have shown that the provisional entity ALCL Hodgkin-like, as designated in the Revised

European-American classification of lymphoid neoplasms, is now thought to be classical Hodgkin lymphoma in most cases. It also has become clear that ALCL arising in skin is a distinct entity, now designated as cutaneous ALCL. As a result, in the 2001 WHO classification, the category ALCL refers to systemic neoplasms of T- or null-cell lineage.[2] This group represents approximately 2% of all non-Hodgkin lymphomas and approximately 20% of all T-cell lymphomas in North America and is less frequent in Europe and Asia.[6]

Although diagnostic parameters for the diagnosis of ALCL have substantially streamlined the ALCL category in the WHO classification, ALCL remains heterogeneous and includes 2 groups: neoplasms that aberrantly express ALK and others that do not. ALK+ ALCLs represent approximately 50% to 80% of all ALCLs, with the relative frequency highest in young patients.[2] The remaining cases are ALK–. The ALK+ group is relatively homogeneous in that all cases express ALK and have chromosomal abnormalities involving chromosome 2p23, the *ALK* locus. Of these, the t(2;5)(p23;q35) is most common. The group of ALK– ALCLs is heterogeneous at the immunophenotypic and molecular levels and use of this term is controversial.[7]

ALK+ Anaplastic Large Cell Lymphoma

Clinical Features

The clinical manifestations and response to therapy of patients with ALK+ ALCL were not the focus of the Workshop. These data can be found in a number of studies in the literature.[2-4,6,8-10] However, it is recognized that patients with ALK+ ALCL tend to be younger than patients with ALK– ALCL. Most patients with ALK+ ALCL are younger than 40 years, with a male predominance, as shown in the cases submitted to the Workshop **Table 1**. Extranodal

Table 1
Summary of ALK+ ALCL Cases Submitted to the 2005 Society of Hematopathology/European Association for Haematopathology Workshop

Case No./ Sex/Age (y)	Biopsy Site	Immunophenotype		Lineage	ALK Pattern	Molecular or Cytogenetic Data	Unusual Features
		Positive*	Negative†				
7/M/8	LN	CD3 (weak), CD7, CD8, CD30	CD4, CD20, CD79A, TdT	T	N+C	ND	
57/M/16	Infraorbital mass and LN	CD30, CD43, CD45, CD45RO	CD15, CD20, CD68	T	C	*ALK* rearrangement shown by FISH	Subsequent chronic myelogenous leukemia
102/M/32	LN	CD30	CD3, CD15, CD20, CD45, CD45RO, CD79A	Null	C	TPM3-ALK	Variant translocation
106/M/36	Mediastinal soft tissue	CD30	CD2, CD3, CD5, CD15, CD20, CD43, CD45RB	Null	N+C	ND	
114/M/16	Brain	CD30, CD45	CD3, CD5, CD15, CD20, CD56, CD57, CD68, BCL-2, fascin	Null	N+C	ND	CNS involved; ? began in psoas muscle
119/F/31	LN, PB, BM	CD2, CD3, CD4, CD5 (dim), CD8, CD30, EMA	Immunoglobulin, B-cell antigens	T	N+C	t(2;5) by CG	Small cell variant
127/M/12	LN, pleural fluid, CSF, PB, BM	cCD3, CD7, CD13, CD16, CD30, CD43, CD56, TIA-1, EMA	CD2, CD3, CD7, CD15, CD20, CD68	T	N+C	*ALK* rearrangement shown by FISH and t(2;5) by CG	Small cell variant in leukemic phase
130/M/13	LN	CD30, EMA	CD1a, CD3, CD20, CD68	Null (limited workup)	N+C	ND	Small cell and histiocyte-rich variant
132/F/78	Bladder	CD2, CD3, CD4, CD5, TIA-1, granzyme B, EMA	CD7, CD8	T	C	ND	Location and sarcomatoid appearance raised differential diagnosis with inflammatory myofibroblastic tumor
156/M/46	LN	CD3, CD7, CD30, CD43, CD56, granzyme B, EMA (focal)	CD2, CD4, CD5, CD8, CD45, CD68	T	N+C	ND	Monomorphic/small cell variant
165/M/15	Brachial plexus LN	CD5, CD25, CD30	CD56	T	C	*ALK* rearrangement shown by FISH	Brachial plexus neuropathy mimicking Pancoast tumor
211/M/28	LN	CD30, EMA	—	Limited workup	N+C	ND	

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; BM, bone marrow; c, cytoplasmic; CG, conventional cytogenetics; CNS, central nervous system; CSF, cerebrospinal fluid; EMA, epithelial membrane antigen; FISH, fluorescence in situ hybridization; LN, lymph node; N+C, nuclear and cytoplasmic; ND, not done; PB, peripheral blood; TdT, terminal deoxynucleotidyl transferase; TPM, tropomyosin.
* Includes markers assessed by flow cytometric or immunohistochemical studies.
† Nonlymphoid markers tested are not included.

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involvement is common, with the most common sites being skin, soft tissue, bone, and lung.[2-4] ALK+ ALCL can also initially manifest at an extranodal site. It is also recognized that patients with ALK+ ALCL have a favorable prognosis compared with patients with other types of T-cell lymphoma, including ALK– ALCL.[9,10]

Seven cases submitted to the Workshop illustrated unusual clinical manifestations of ALK+ ALCL (cases 57, 106, 114, 119, 127, 132, and 165). Case 57 was a patient with ALK+ ALCL, classical variant, who initially presented with an infraorbital mass and right inguinal lymphadenopathy. Chronic myelogenous leukemia subsequently developed **Image 1**. Cases 106, 114, and 165 were neoplasms that arose at uncommon extranodal sites of involvement. Case 106 manifested with extensive mediastinal and paratracheal lymph nodes. The mediastinum is involved in only a subset of ALCL patients (approximately 10%). This site, being commonly involved in classical Hodgkin lymphoma, highlights issues of differential diagnosis. Cases 114, 132, and 165 involved the brain **Image 2**, bladder **Image 3**, and brachial plexus region **Image 4**, respectively. The latter case caused neuropathy imparting a Pancoast tumor–like manifestation. Cases 119 and 127 **Image 5** had or subsequently developed marked leukemic involvement.

Histologic Features

Although the name ALCL is used in the WHO classification, it is recognized that the designation has its shortcomings because variants of ALCL are now recognized (eg, small cell) in which most of the neoplastic cells are neither large nor anaplastic.[2-4,8,9,11,12]

ALK+ ALCLs can exhibit a wide histologic spectrum. In the classical variant, as originally described by Stein et al[1] and illustrated by a number of cases submitted to the

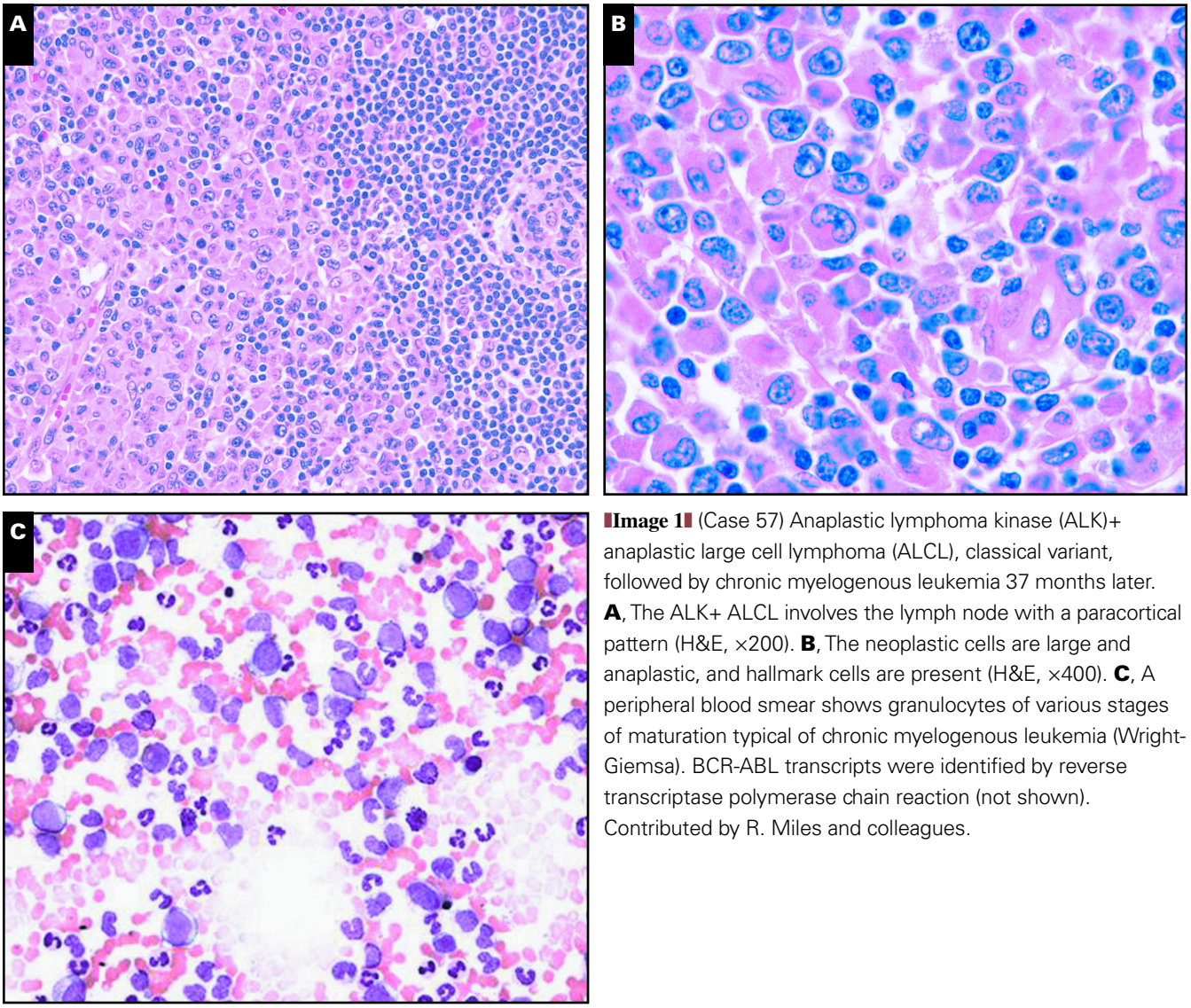

Image 1 (Case 57) Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma (ALCL), classical variant, followed by chronic myelogenous leukemia 37 months later. **A**, The ALK+ ALCL involves the lymph node with a paracortical pattern (H&E, ×200). **B**, The neoplastic cells are large and anaplastic, and hallmark cells are present (H&E, ×400). **C**, A peripheral blood smear shows granulocytes of various stages of maturation typical of chronic myelogenous leukemia (Wright-Giemsa). BCR-ABL transcripts were identified by reverse transcriptase polymerase chain reaction (not shown). Contributed by R. Miles and colleagues.

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Workshop, ALCL cells are anaplastic (Images 1 and 4) **Image 6**. The neoplastic cells grow cohesively and preferentially involve lymph node sinuses, particularly in lymph nodes not involved extensively (Image 6). With greater involvement, ALCL replaces the paracortical regions or may diffusely replace lymph node architecture. Cytologically, the neoplastic cells are large, bizarre, and irregularly shaped and often have polylobated nuclei. The nuclear chromatin is vesicular with variably prominent nucleoli. The tumor cell cytoplasm is abundant and often basophilic. So-called hallmark cells are usually present. These cells have a horseshoe- or kidney-shaped nucleus that partially or completely surrounds a clear, or more eosinophilic, paranuclear (Golgi) area (Image 1). It is important to note that smaller neoplastic cells with some similarity to hallmark cells are also frequently present, and thus the neoplastic cells exhibit a spectrum of cytologic atypia. This spectrum is helpful in distinguishing ALCL from classical Hodgkin lymphoma. The classical variant represents approximately 70% of all ALK+ ALCL cases.

Other histologic variants of ALK+ ALCL are described.[2-4,10] These include the lymphohistiocytic (5%-10%), small cell (5%-10%) **Image 7**, and sarcomatoid (<1%) (Image 3) variants. A monomorphic variant **Image 8** of ALCL is also described by some authors, although these cases are not grouped as a separate variant in the WHO classification. These neoplasms are more difficult to recognize without knowledge of CD30 or ALK expression. The lymphohistiocytic variant is composed of relatively few neoplastic cells associated with numerous reactivelymphocytes and histiocytes. In the small cell variant, large neoplastic cells are infrequent, and most of the neoplastic cells are small. In the sarcomatoid variant, the neoplastic cells are spindle-shaped and resemble sarcoma.

A few cases submitted to the Workshop had highly unusual features and were diagnostically challenging.

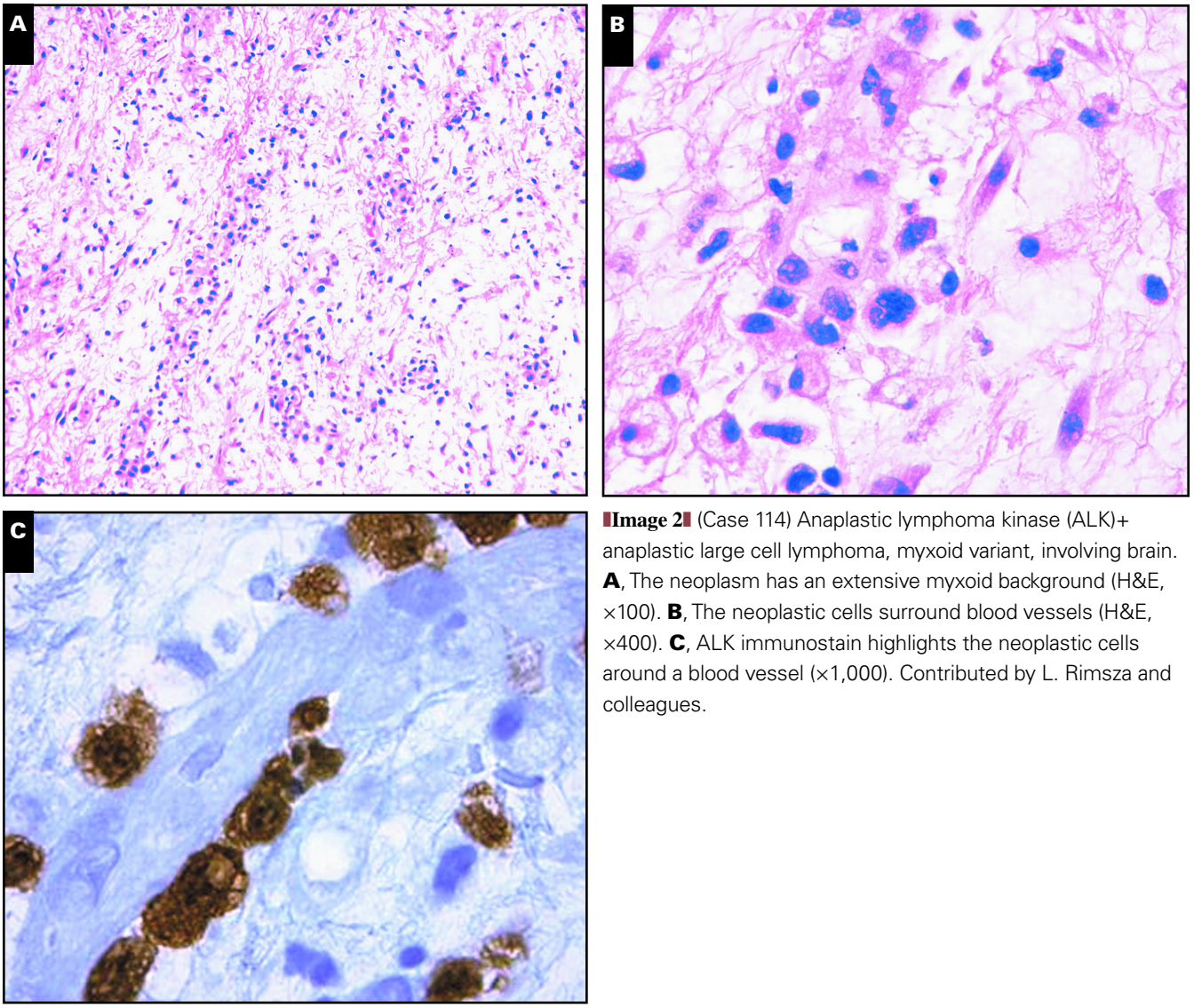

Image 2 (Case 114) Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma, myxoid variant, involving brain. **A**, The neoplasm has an extensive myxoid background (H&E, ×100). **B**, The neoplastic cells surround blood vessels (H&E, ×400). **C**, ALK immunostain highlights the neoplastic cells around a blood vessel (×1,000). Contributed by L. Rimsza and colleagues.

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Case 132, which has been reported previously,[13] was considered the sarcomatoid variant (Image 3). This neoplasm had a nodular fasciitis–like appearance and arose in the bladder wall. The location and the histologic findings raised the differential diagnosis with inflammatory myofibroblastic tumor (IMT). Case 114 involved the brain and had an abundant myxoid background (Image 2). Cases 114 and 132 were shown immunohistochemically to be positive for CD30 and ALK, supporting the diagnosis of ALK+ ALCL. Case 127, an ALK+ ALCL in leukemic phase, was unusual at the molecular level because it carried the t(2;5)(p23;q35) and t(3;8)(q26.2;q24), the latter shown to involve MYC at 8q24 by fluorescence in situ hybridization (FISH).

Immunophenotypic Features

The value of CD30 and ALK expression for establishing the diagnosis of ALK+ ALCL cannot be overemphasized (Images 2, 3, and 6). In ALCL, CD30 is expressed strongly by the neoplastic cells in a characteristic membranous and paranuclear (Golgi) pattern (target-like appearance).[2-4] ALK overexpression in ALK+ ALCL can be nuclear and cytoplasmic, cytoplasmic only, and rarely membranous. However, CD30 and ALK (rarely) are not specific for ALCL.

As currently defined, ALK+ ALCL can be of T- or null-cell lineage.[2] Most of the null-cell tumors have molecular evidence supporting T-cell origin (ie, T-cell receptor gene rearrangements), but some ALK+ ALCLs do not, and these tumors could possibly be of natural killer cell origin.

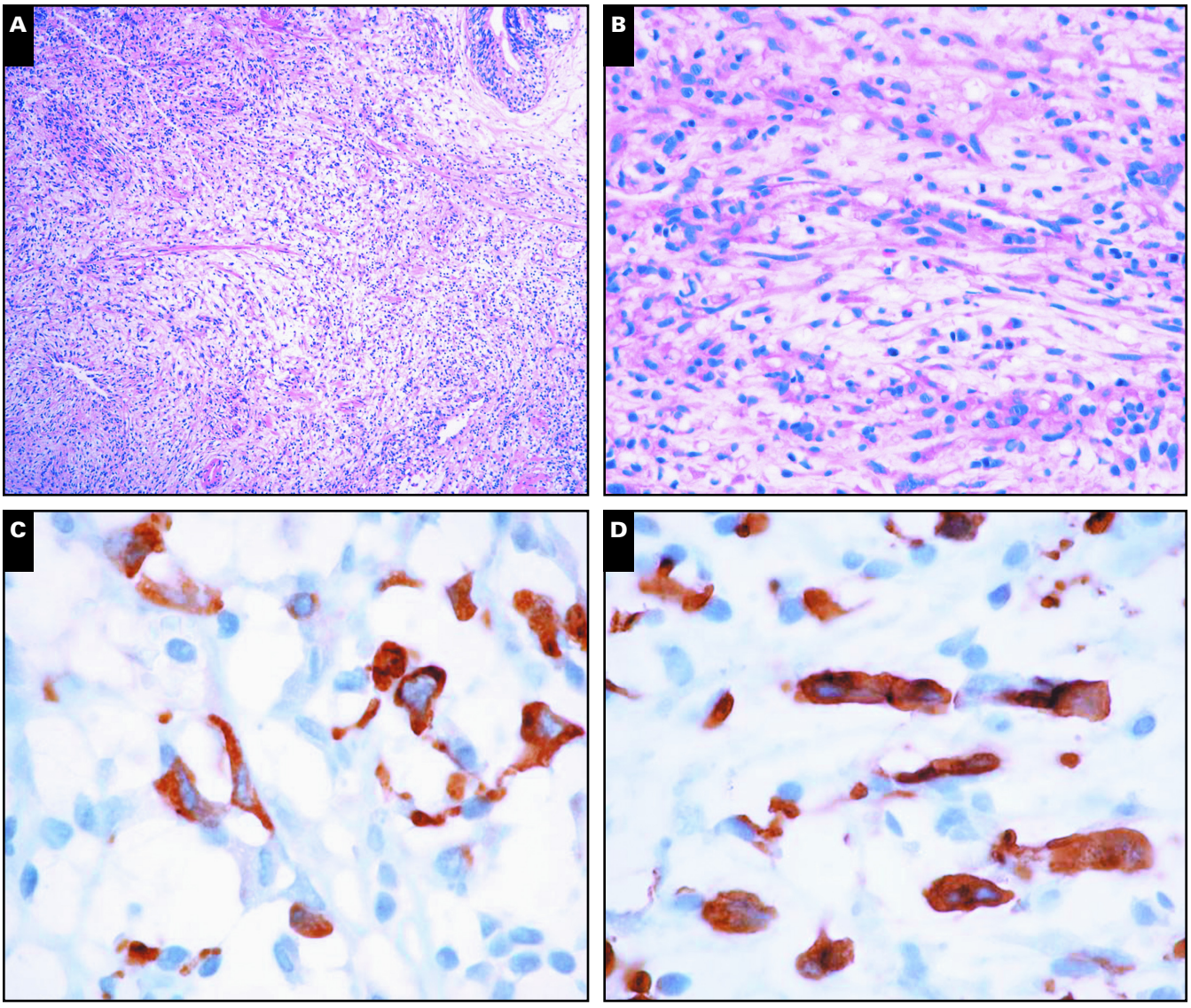

Image 3 (Case 132) Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma, sarcomatoid variant. **A**, The neoplasm involved the bladder wall. Benign urothelium is seen in the upper right side of the image (H&E, ×100). **B**, The neoplastic cells are spindled within a myxoid background (H&E, ×200). **C** and **D**, The neoplastic cells are positive for CD30 (**C**, ×1,000) and ALK (**D**, ×1,000). Contributed by P. Gaulard and colleagues.

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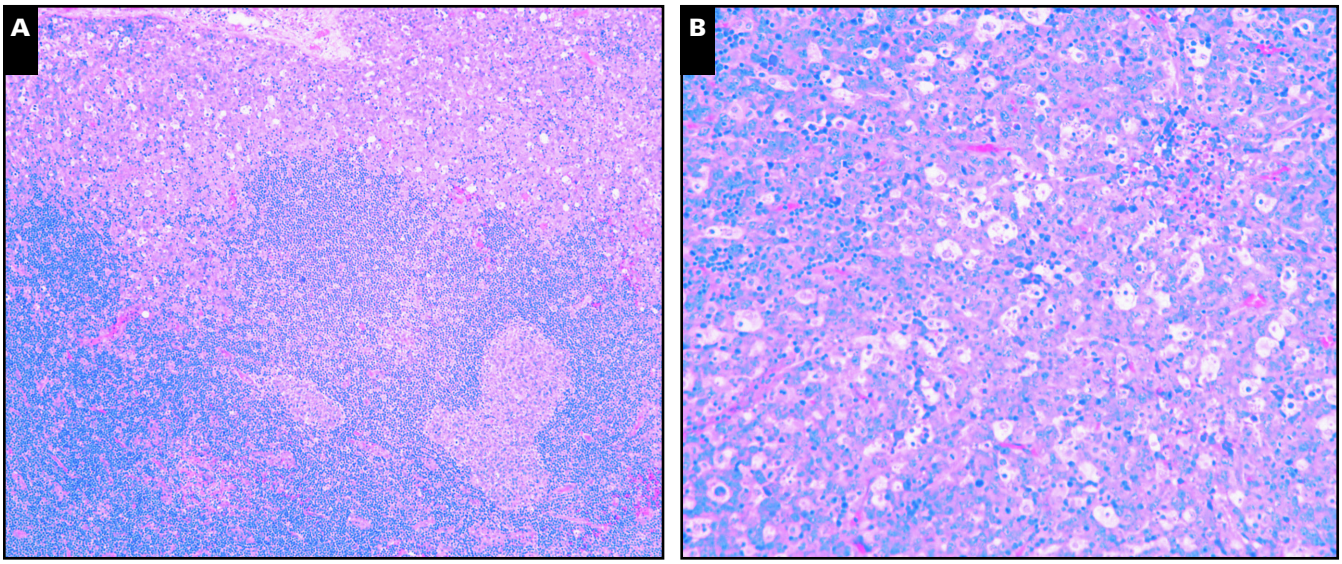

Image 4 (Case 165) Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma, classical variant. The patient sought care because of brachial plexus neuropathy. **A**, In this field, the neoplasm preferentially involves the subcapsular sinus (H&E, ×100). **B**, A prominent starry-sky pattern is shown (H&E, ×200). ALK immunostaining showed a cytoplasmic pattern consistent with a variant translocation (not shown). Contributed by S. Cope-Yokoyama and colleagues.

In T-cell lineage ALK+ ALCL, an aberrant T-cell immunophenotype is common, and this was true for many cases submitted (cases 7, 102, 106, 114, 127, 132, and 156). These tumors often do not express CD3, CD5, or T-cell receptors suggestive of defective T-cell signaling.[14] CD4 is expressed more often than CD8, and a subset of neoplasms is negative for CD4 and CD8.[3]

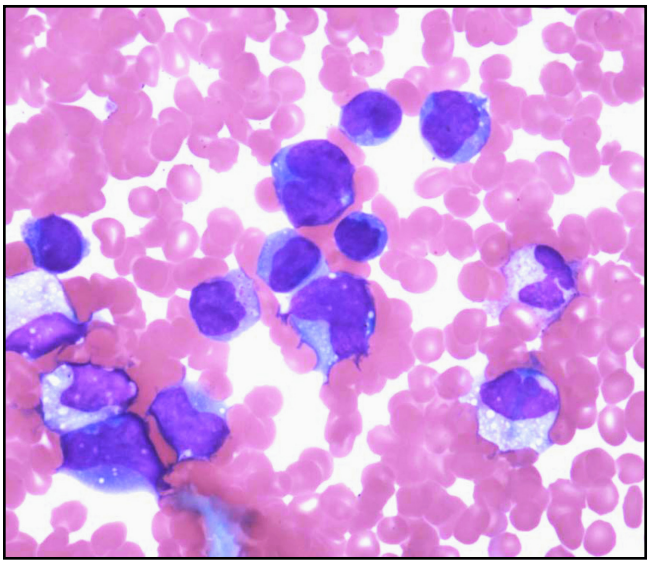

Image 5 (Case 127) Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma, in leukemic phase. Peripheral blood smear showing numerous neoplastic cells (Wright-Giemsa, ×1,000). Conventional cytogenetic analysis showed the t(2;5)(p23;q35) and t(3;8)(q26.2;q24). Fluorescence in situ hybridization analysis with break-apart probes showed *ALK* and *MYC* rearrangements. Contributed by B. Alobeid and colleagues.

ALK+ ALCL commonly expresses cytotoxic molecules, such as granzyme B, perforin, and TIA-1.[2,15] However, many of the ALK+ ALCL cases submitted did not have these data, suggesting that many hematopathologists do not routinely assess for cytotoxic molecule expression. These neoplasms usually have a high proliferation rate and express activation markers. Virtually all ALK+ ALCLs are negative for BCL-2 and have a high apoptotic rate.[16] Most ALK+ ALCLs express clusterin, but clusterin also can be expressed uncommonly in other lymphoid neoplasms.[17,18] Most cases of ALK+ ALCL are negative for CD15 and lack evidence of Epstein-Barr virus infection.[19]

Immunohistochemical vs Flow Cytometric Immunophenotyping: Which Technique Is Best Suited to the Task?

Immunohistochemical analysis is well suited to the analysis of ALK+ ALCL tissue specimens, and many pathologists consider this approach the method of choice. Most of the antibodies essential for diagnosis of ALK+ ALCL are reactive in routinely fixed, paraffin-embedded tissue sections, and some of these antibodies (eg, ALK and granzyme B) are optimized for this approach to immunophenotypic diagnosis.

An obvious drawback to immunohistochemical analysis is that it is not well suited to the analysis of fluid specimens, such as body fluids, peripheral blood, or bone marrow aspirate specimens, or samples obtained by fine-needle aspiration.

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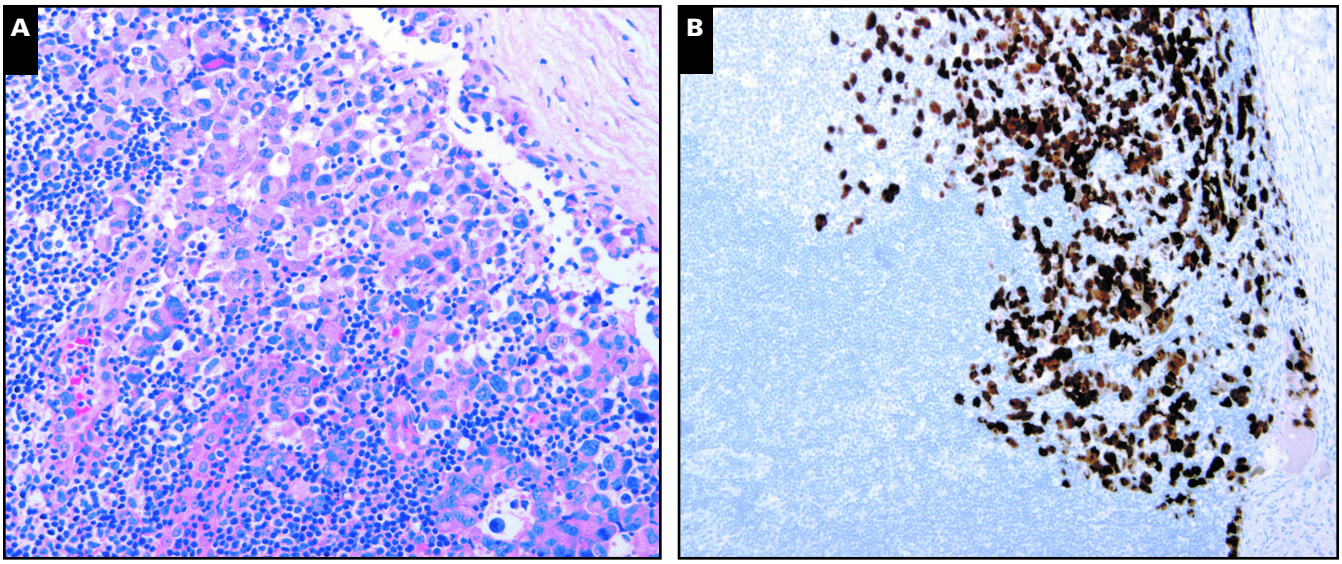

Image 6 (Case 211) **A**, Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma, classical variant. The neoplasm involves the subcapsular sinus (H&E, ×200). **B**, ALK immunostain has a nuclear and cytoplasmic pattern and highlights sinusoidal involvement and invasion of germinal centers (×200). Contributed by M. Mollejo.

A second drawback is that immunohistochemical analysis is relatively insensitive compared with flow cytometry. Thus, dim antigen expression detected by flow cytometric immunophenotyping can often be negative by immunohistochemical analysis. For example, CD45 (leukocyte common antigen [LCA]) is commonly positive in ALK+ ALCL assessed by flow cytometry but can be negative in a subset of cases by immunohistochemical analysis.

Flow cytometric immunophenotyping has been used to diagnose ALK+ ALCL and has many advantages well known to readers.[20,21] Turnaround time is fast, results are sensitive and quantitative, and numerous antibodies can be used that are

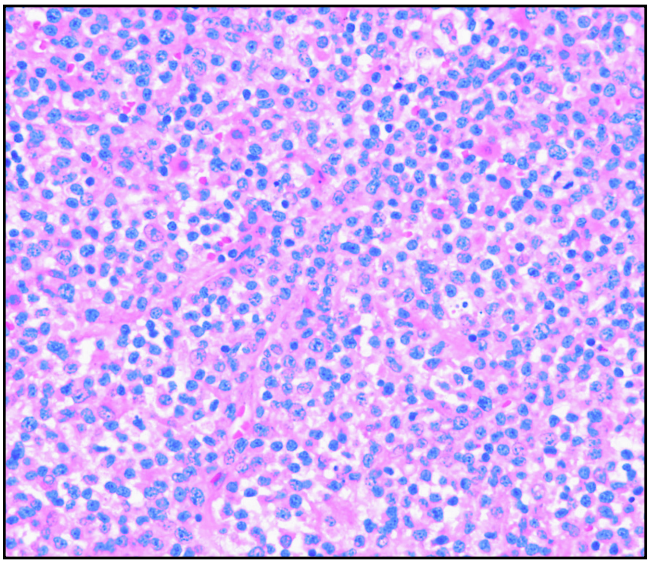

Image 7 (Case 7) Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma, small cell variant. An inguinal lymph node was completely effaced by neoplastic small to intermediately sized cells (H&E, ×400). The ALK immunostaining pattern was nuclear and cytoplasmic (not shown). Contributed by A. Hassan.

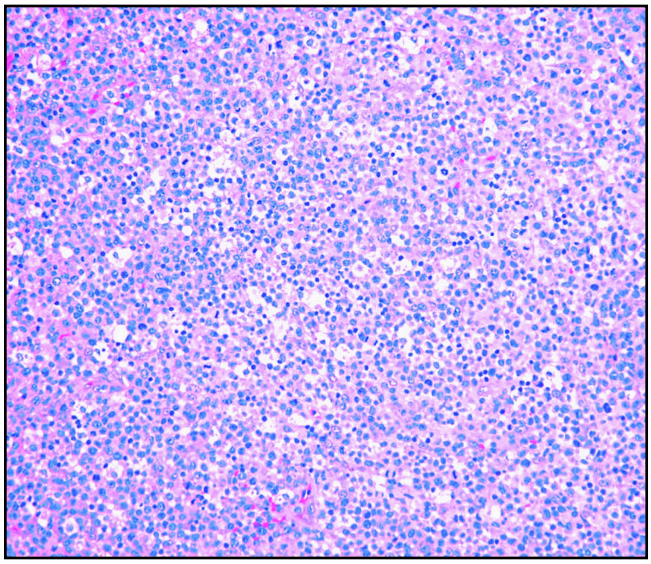

Image 8 (Case 156) Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma, monomorphic variant. The neoplastic cells are of intermediate to large size and monomorphous (H&E, ×400). The ALK immunostaining pattern was nuclear and cytoplasmic (not shown). Contributed by P.S. Lee and colleagues.

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not available for immunohistochemical analysis of fixed tissues. In 1 study, Juco and colleagues[20] established the diagnosis of ALCL in 19 cases by using flow cytometry. All cases had an aberrant T-cell immunophenotype with the following frequency of T-cell antigen expression: CD2, 71%; CD4, 63%; CD3, 32%; CD7, 32%; CD5, 26%; and CD8, 21%.

One potential drawback to a flow cytometric approach is that certain antigens are expressed intracellularly (eg, ALK and cytotoxic molecules) and require cell permeabilization for analysis, although many flow cytometry laboratories do this procedure routinely. Another potential drawback is that flow cytometric immunophenotyping has shown that ALCLs express antigens, not usually assessed by immunohistochemical analysis, that can cause diagnostic confusion. Of these, the myeloid-associated antigens CD11b, CD13, CD15, and CD33 can be expressed by ALK+ ALCL, with CD13 being positive most often[20,21] **Image 9**. The neoplastic cells in CD45 vs side scatter plots also appear in the area where monocytes reside. Thus, the immunophenotypic data can be misinterpreted as support for myeloid-monocytic sarcoma. Another potential drawback is that the neoplastic cells are fragile and can be lost or underrepresented in cell suspensions during processing.

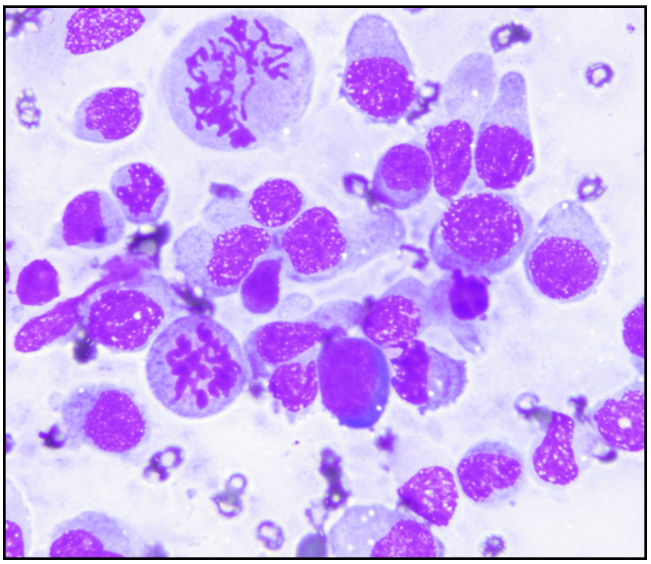

Image 9 Fine-needle aspiration smear of anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma (Wright-Giemsa, ×1,000). Flow cytometric immunophenotyping of this specimen showed that the neoplastic cells were positive for CD4, CD11c, CD13, CD14 (dim), and CD45 and negative for CD3, CD7, CD8, CD10, CD19, CD20, CD33, CD34, and CD56. These results led to a preliminary diagnosis of myeloid sarcoma at the submitting institution. Excisional biopsy showed ALK+ anaplastic large cell lymphoma. The ALK pattern was nuclear and cytoplasmic. (This case was not contributed to the Workshop and was provided courtesy of S. Konoplev.)

Is CD30 Expression Specific for ALK+ ALCL?

CD30 is a transmembrane receptor and a member of the tumor necrosis factor superfamily that is normally expressed by activated T cells.[22] Binding of CD30 to its ligand, CD30L, elicits numerous cellular responses, but its exact function in the pathogenesis of ALCL is unknown.

As is well known to readers, CD30 is not specific for ALCL. CD30 expression was originally described as a marker relatively specific for Reed-Sternberg and Hodgkin cells of classical Hodgkin lymphoma.[23] Subsequently, other types of non-Hodgkin lymphoma, reactive immunoblasts, and non-lymphoid neoplasms were shown to express CD30.[3,4] However, as mentioned, the staining pattern for CD30 in ALCL is distinctive, being intense with a membranous and paranuclear pattern (target-like appearance). Other non-ALCL neoplasms may express CD30 similarly, but usually CD30 staining is less intense and/or less uniform.

What Is the Normal Expression Pattern and Function of ALK?

ALK, also known as CD246, is a tyrosine kinase that belongs to the insulin receptor superfamily.[24] Full-length ALK has an extracellular ligand binding region, a transmembrane region, and a cytoplasmic domain. The cytoplasmic portion of ALK includes the catalytic domain. The catalytic domain can form homodimers (homotrimers, etc) with other ALK molecules and thereby undergo phosphorylation (activation).

ALK is normally expressed by a small subset of cells in the central and peripheral nervous systems of adults. Pleiotrophin and midkine have been suggested as possible ligands of ALK, but it seems likely that other ligands exist. The normal functions of ALK remain unclear.

Is ALK Expression Specific for ALK+ ALCL?

Other pathologic lesions have been identified that overexpress ALK. These lesions include some solid tumors, a subset of IMTs, and a rare subtype of DLBCL.

ALK expression has been shown in cell lines derived from neuroblastoma, neuroectodermal tumors, glioblastoma, melanoma, and rhabdomyosarcoma.[4,25] ALK is also expressed in most primary neuroblastomas and a subset of rhabdomyosarcoma tumors. In some of these cell lines and in both neuroblastoma and rhabdomyosarcoma tumors, ALK has been shown to be full length and unphosphorylated (ie, inactive). Because ALK is normally expressed in a subset of cells in the central and peripheral nervous systems, one possible explanation is that ALK is present in these tumors because of its presence in their cell of origin and is not involved in pathogenesis (ie, an innocent bystander). In rhabdomyosarcoma, ALK is more often expressed in the alveolar type, approximately 45%, compared with the embryonal type, 15%.[26]

A subset of IMTs, approximately one third, overexpresses ALK and has been shown to have *alk* locus abnormalities

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by conventional cytogenetics or FISH.[27,28] These lesions tend to occur in younger patients, more often boys, and may recur more frequently than histologically similar lesions without ALK expression.[27] The translocations involving *alk* that occur in IMTs involve nonmuscle tropomyosins 3 and 4 and result in *tpm3-alk* and *tpm4-alk* chimeric fusions.[28]

Rare cases of DLBCL are reported that express ALK. Histologically, these tumors commonly show sinusoidal invasion, immunoblastic cytologic features, and plasmacytoid differentiation. Immunophenotypically, these tumors express IgA, epithelial membrane antigen, and CD4, but lack CD30, pan–T-cell antigens, and cytotoxic molecules. These cases can be divided into 2 groups. In the first group, ALK+ DLBCL can carry the t(2;5), as is commonly seen in ALK+ ALCL.[29] In the second group, cases of ALK+ DLBCL carry the t(2;17)(p23;q23) involving the *alk* and clathrin genes.[30] The original description of the latter group suggested that these neoplasms express full-length ALK.[31] Although this may still be true in a subset of cases, more recent studies have shown that a subset of these neoplasms carry the t(2;17). Because clathrin is a component of the membranes of cytoplasmic vesicles, ALK+ DLBCL carrying the t(2;17) exhibits a distinctive pattern of ALK staining that is cytoplasmic and granular.[30]

If ALK Expression Is Not Specific, How Can It Be Used to Define ALK+ ALCL?

Although ALK expression is an extremely important feature in the diagnosis of ALK+ ALCL, in fact, ALCL is defined by more than ALK expression. ALCL is a neoplasm of CD30+ lymphoid cells of T- or null-cell lineage that usually has distinctive histologic features, including sinusoidal invasion, anaplasia, and hallmark cells. These neoplasms also usually express cytotoxic molecules. Within this context, positivity for ALK defines a distinctive group of ALCLs with important prognostic implications.

The expression of ALK in other entities, although potentially misleading, is usually not a problem in diagnosis because the morphologic and immunophenotypic features (eg, CD30–) of these other entities allow their recognition.

Molecular Findings

To date, at least 9 chromosomal translocations involving the *alk* locus at chromosome 2p23 have been characterized in ALK+ ALCL **Table 2**.[24,32] All translocations involve *alk* and result in the catalytic domain of ALK being joined with a partner, resulting in ALK phosphorylation and constitutive activation.

The t(2;5)(p23;q35) is, by far, the most common translocation, occurring in approximately 75% to 80% of ALK+ ALCL cases.[24,33] In this translocation, the nucleophosmin (*npm)* gene on chromosome 5q35 and the *alk* gene on chromosome 2p23 are disrupted and recombined to form a fusion gene. The resultant novel fusion protein, NPM-ALK, is composed of the amino-terminal portion of NPM fused to the carboxy-terminal portion of ALK. The *npm* portion of the fusion gene has a strong promoter driving overexpression of NPM-ALK. Normal NPM is a ubiquitously expressed protein that has many functions, including ribosomal assembly, cytoplasmic-nuclear shuttling of proteins, centrosome duplication, and p53 regulation.[34]

Table 2
Anaplastic Lymphoma Kinase Partners in Anaplastic Large Cell Lymphoma

Translocation	Partner
t(2;5)(p23;q35)	Nucleophosmin
t(1;2)(p25;p23)	Tropomyosin 3
t(2;3)(p23;q21)	TFG
inv(2)(p23q35)	ATIC
t(2;17)(p23;q23)	Clathrin heavy chain
t(2;X)(p23;q11-12)	Moesin
t(2;17)(p23;q25)	ALO17
t(2;22)(p23;q11.2)	MYH9
t(2;19)(p23;q13.1)	Tropomyosin 4

A number of other uncommon chromosomal abnormalities, mostly translocations, involve the *alk* locus and result in ALK expression **Image 10**. These variant abnormalities occur in approximately 20% to 25% of ALK+ ALCL cases. It also seems likely that additional but infrequent chromosomal translocations involving *alk* will be recognized in the future.

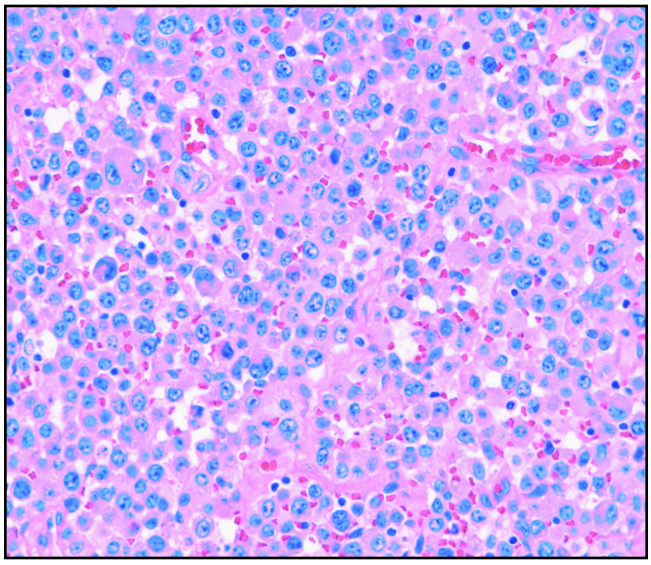

Image 10 (Case 102) Anaplastic lymphoma kinase (ALK)+ anaplastic large cell lymphoma, classical variant, associated with tropomyosin (TPM)3-ALK fusion (H&E, ×400). TPM3 was identified in this case by 5'-RNA ligase-mediated rapid amplification of complementary DNA ends. Contributed by M. Lim and colleagues.

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Which Method Is Best for Proving an alk *Molecular Abnormality in a Case of ALK+ ALCL?*

A number of methods can be used for demonstrating *alk* abnormalities in ALK+ ALCL. Conventional cytogenetic analysis allows one to detect the t(2;5) or any other translocation or inversion involving *alk*, as well as additional abnormalities, if present. Thus, this method provides the most information. The major drawback is that a fresh tissue sample is needed for these studies, and lymphomas are often not sent for cytogenetic analysis routinely. FISH using a break-apart probe around the *alk* locus is commercially available and can be applied to fixed, paraffin-embedded tissue samples. The major drawback to this approach is that the partner gene cannot be identified. Southern blot hybridization analysis using an *alk* probe can be used to gain information similar to that provided by FISH, but this requires fresh or frozen tissue samples and is technically laborious. Reverse-transcriptase or long-range polymerase chain reaction (PCR) can be used to detect the t(2;5), and the former can be done using formalin-fixed, paraffin-embedded tissue samples, but neither method will detect the variant translocations.[35] Additional primers can be designed to detect the uncommon variant translocations, but this increases the labor and complexity of testing, and the yield is low. PCR methods have a greater role in the assessment of minimal residual disease.

Do the Variant alk *Abnormalities Have Prognostic Significance?*

As stated, patients with ALK+ ALCL have a better prognosis than patients with ALK– ALCL, with the latter more akin to peripheral T-cell lymphoma (PTCL), unspecified. In 1 study, Falini and colleagues[36] showed that patients with variant *alk* abnormalities have a good prognosis, similar to (or better than) that of patients with t(2;5)+ ALK+ ALCL.

What Can the ALK Immunostaining Pattern Tell Us About the Molecular Abnormalities?

ALK overexpression in lymphomas is abnormal[5] and reliably predicts the presence of *alk* molecular alterations. The immunostaining pattern of ALK also correlates with molecular abnormalities.[4,10,22] NPM normally shuttles proteins from the cytoplasm to the nucleus. In the t(2;5), although the fusion protein does *not* retain the nucleolar localization signal of NPM, most likely NPM-ALK forms heterodimers with wild-type NPM and enters the nucleus via this mechanism. Thus, in a t(2;5)+ case of ALCL, ALK-1 immunostaining is cytoplasmic and nuclear (Image 6). In an ALK+ ALCL with a molecular abnormality other than the t(2;5), the partner protein is not NPM, and the pattern of ALK-1 immunostaining is cytoplasmic. In addition, a rare *alk* translocation uses moesin as a partner. Because moesin is a part of the plasma membrane, ALK expression in these rare tumors has a membranous pattern.

Is ALK Immunostaining as Good as Molecular Techniques for the Diagnosis of ALK+ ALCL?

Conventional cytogenetic analysis provides the most information and is ideal. However, because fixed, paraffin-embedded tissue is often the only specimen available, ALK immunostaining is popular. The presence of ALK overexpression has similar meaning to a positive FISH result and is convenient, less laborious, and usually faster. In other words, ALK overexpression and FISH using an *alk* locus break-apart probe detect all *alk* locus abnormalities. Most of the PCR approaches only detect the t(2;5) or a few of the variants, and, therefore, ALK immunostaining or FISH is better for initial diagnosis.

What Common Features Do the Partners of ALK Share?

There are at least 4 common features: (1) The partner protein is normally widely expressed. (2) The subcellular distribution of ALK is determined by the normal location of the partner. (3) Most partners have oligomerization domains allowing ALK to undergo dimerization and become phosphorylated. (4) All partners, by facilitating ALK overexpression and dimerization, result in activation of downstream signaling pathways and neoplastic transformation. The downstream pathways activated are beyond the scope of this review, and readers are referred to other sources.[24,33,37]

What Is the Relative Frequency of ALK+ ALCL?

The relative frequency of ALK+ ALCL varies considerably in the literature. In the WHO classification, it is stated that 60% to 85% of ALCL cases are ALK+.[2] Other studies have reported a frequency of approximately 40% to 50%.[9,16] There are at least 2 explanations for the varying frequencies. First, because ALK+ ALCL occurs more often in young patients, the median age of the patient population assessed will influence the frequency of ALK overexpression in ALCL cases. Second, the definition of ALK– ALCL used by the pathologist will also affect the relative frequency of ALK+ ALCLs. If a stricter definition of ALK– ALCL is used, with many CD30+ and ALK– tumors designated as PTCL, unspecified, the relative frequency of ALK+ ALCL is increased.

ALK– Anaplastic Large Cell Lymphoma

What Is the Definition of ALK– ALCL?

As became clear during the session, there is no consensus for the definition of ALK– ALCL. Perhaps the strictest definition articulated at the meeting is that ALK– ALCL should very closely mimic ALK+ ALCL in its histologic and immunophenotypic findings except, of course, be ALK–. Others had a less strict definition, with the ALK– ALCL category including

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anaplastic T- or null-cell neoplasms that strongly and uniformly expressed CD30 and had some of the histologic features of ALK+ ALCL.

Not surprisingly, the use of the designation ALK– ALCL was also controversial during the session for the reasons stated previously in the WHO classification and by others in the literature. One school of thought, apparently the predominant opinion of the session participants, is that ALK– ALCL is not distinctive at the immunophenotypic or genetic level and, therefore, is best considered a variant of PTCL, unspecified. The other school of thought expressed during the session is that the histologic findings of ALK– ALCL are distinctive and justify the use of this term. Otherwise, the distinctive histologic findings of these neoplasms become lost in the PTCL, unspecified category.

In the following, we briefly review the clinicopathologic features of neoplasms that have been designated as ALK– ALCL in the literature.

Clinical Features

Unlike ALK+ ALCL, ALK– ALCL occurs in relatively older patients, and there is no sex predominance as shown by many of the cases submitted **Table 3**.[2,3] Extranodal involvement can occur but is relatively less common in patients with ALK– ALCL. The clinical manifestations are heterogeneous. Many patients have systemic (B) symptoms, a high International Prognostic Index, and an aggressive clinical course.[2,16,38] However, a subset of patients has a less aggressive course. A number of studies have shown that patients with ALK– ALCL have a worse prognosis than patients with ALK+ ALCL.[8,9,11]

Histologic Features

Cases of ALK– ALCL exhibit a spectrum of histologic findings.[2,38] The most common variant closely mimics the classical variant of ALK+ ALCL. These ALK– neoplasms can exhibit a cohesive growth pattern and extensive sinus involvement and are composed of anaplastic cells **Image 11**. In fact, the degree of anaplasia is often greater in ALK– ALCL than in ALK+ ALCL. Hallmark cells can be identified in many cases of ALK– ALCL, but they are usually less common than in ALK+ ALCL.

In general, it is more difficult to recognize the nonanaplastic histologic variants of ALK– ALCL than it is to recognize the classical variant. In part, this is because CD30 expression is not specific for ALCL and ALK overexpression

Table 3
Summary of ALK-ALCL Cases Submitted to the 2005 Society of Hematopathology/European Association for Haematopathology Workshop

Case No./ Sex/Age (y)	Biopsy Site	Immunophenotype: Positive	Immunophenotype: Negative	Lineage	Molecular or Cytogenetic Data	Unusual Features	Panel Diagnosis
35/M/22	Mediastinal mass	CD4, CD8, CD15 (focal), CD30, CD45, EMA, p53	CD3, CD5, CD10, CD20,CD23	T	ND	CD15+/CD30+; overlaps with HL	ALK– ALCL
43/M/58	LN	CD2, CD3, CD4, CD15, CD30, CD43, CD45RB	CD5, CD7, CD8, EMA, EBER	T	*TCR* gene rearranged; cytogenetics: del(2q22)add(6p25)	CD15+	ALK– ALCL
166/F/45	Breast	CD15, CD30, CD43	CD3, CD5, CD20, CD45, CD45RO, CD68, CD117, TIA-1	Null	*TCR* gene rearranged	CD15+/CD45–; overlaps with HL	ALK– ALCL
201/M/55	LN	cCD2, CD4 (rare), CD15, CD30, CD43, CD45RO, TIA-1, granzyme B, clusterin, EBER	CD3, CD5, CD7, CD8, CD20, CD45, CD79A, EMA	T	*TCRγ* gene rearranged	CD15+/CD30+/ CD45–; overlaps with classical HL	ALK– ALCL
216/F/50	LN	CD4, CD30, CD43, CD45	CD2, CD3, CD5, CD7, CD15, CD20, EMA, κ, λ, PAX5, CD138, EBER	T	*TCR* gene rearranged		ALK– ALCL vs PTCL
4/M/ "elderly"	LN	CD3, CD4, CD5, CD30, CD43, CD45, BF-1	CD8, CD10, CD15, CD20, CD56, CD79A, fascin, EMA, TIA-1, EBV, LMP	T	ND		PTCL
69/M/31	Chest wall mass and LN	CD3, CD4, CD8 (subset), CD30, clusterin	CD15, CD68, EMA, EBER, clusterin	T	*TCR* gene rearranged; cytogenetics: no t(2;5)	HIV+; features of lymphohistiocytic variant of ALCL	PTCL
190/M/53	LN	CD2, CD3, CD4, CD5, CD7, CD15, CD25, CD30, EMA	CD45RB, clusterin, granzyme B, TIA-1, EBER	T	*TCR* gene rearranged	CD15+/CD30+/CD45–; CD15 acquired at relapse; overlaps with classical HL	PTCL

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; c, cytoplasmic; EBER, EBV-encoded RNA; EBV, Epstein-Barr virus; EMA, epithelial membrane antigen; HL, Hodgkin lymphoma; LMP, latent membrane protein; ND, not done; PTCL, peripheral T-cell lymphoma; TCR, T-cell receptor.

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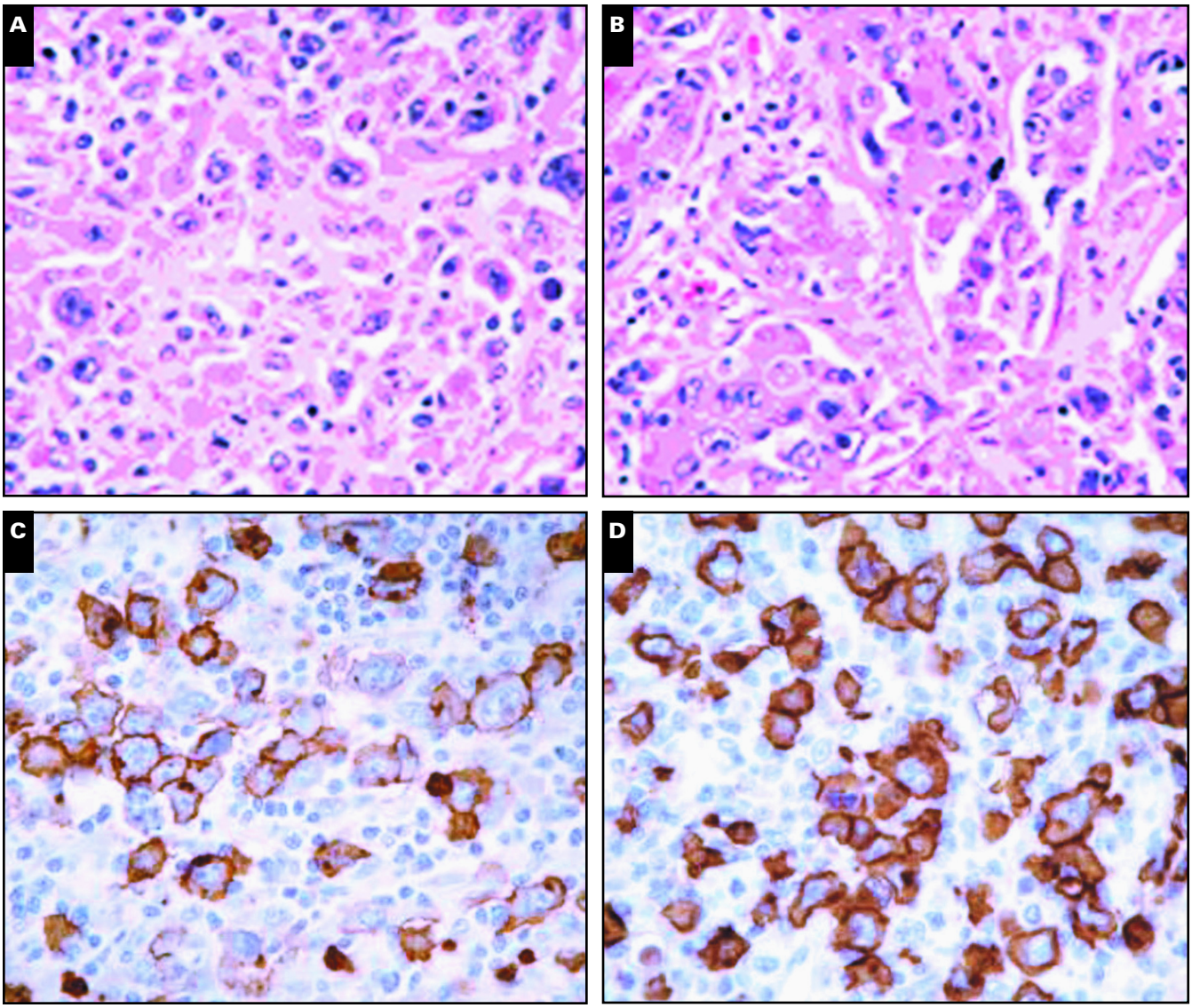

Image 11 (Case 201) Anaplastic lymphoma kinase (ALK)– anaplastic large cell lymphoma in a 55-year-old man with supraclavicular and axillary lymphadenopathy. **A** and **B**, The neoplastic cells were large and anaplastic (**A**, H&E, ×400; **B**, H&E, ×400). **C**-**F**, Immunohistochemical analysis showed that the neoplastic cells were positive for CD15 (**C**, ×400) and CD30 (**D**, ×400) and negative for CD3 (**E**, ×400) and CD45 (**F**, ×400).

is not present to confirm the diagnosis. For example, distinguishing the lymphohistiocytic variant of ALK– ALCL from a CD30+ histiocyte-rich PTCL, unspecified can be problematic. Clusterin expression may be useful to favor ALK– ALCL in this instance.

Immunophenotypic Features

The immunophenotype of ALK– ALCL shares many features with ALK+ ALCL.[2,8,16] In T-cell ALK– ALCLs, an aberrant T-cell immunophenotype is common, and these neoplasms are commonly negative for pan–T-cell antigens (eg, CD3 and T-cell receptors).[14] These tumors also usually have a high proliferation rate and express activation markers, similar to ALK+ ALCL. ALK– ALCL also commonly expresses cytotoxic molecules, in approximately half of the cases, although less frequently than ALK+ ALCL cases.[2,38] Clusterin is expressed at similar frequency in ALK+ and ALK– ALCL,[17,18] and some participants in the Workshop suggested that clusterin was helpful for distinguishing ALK– ALCL from PTCL, unspecified.

However, there are also immunophenotypic differences between ALK+ and ALK– ALCL. Many ALK– ALCL cases express BCL-2, unlike ALK+ ALCL.[16,37] ALK– ALCL can be positive for CD15, and 5 cases of ALK– ALCL submitted to the Workshop were CD15+ (Image 11) (Table 3). Three of these cases were also negative for LCA (CD45), overlapping

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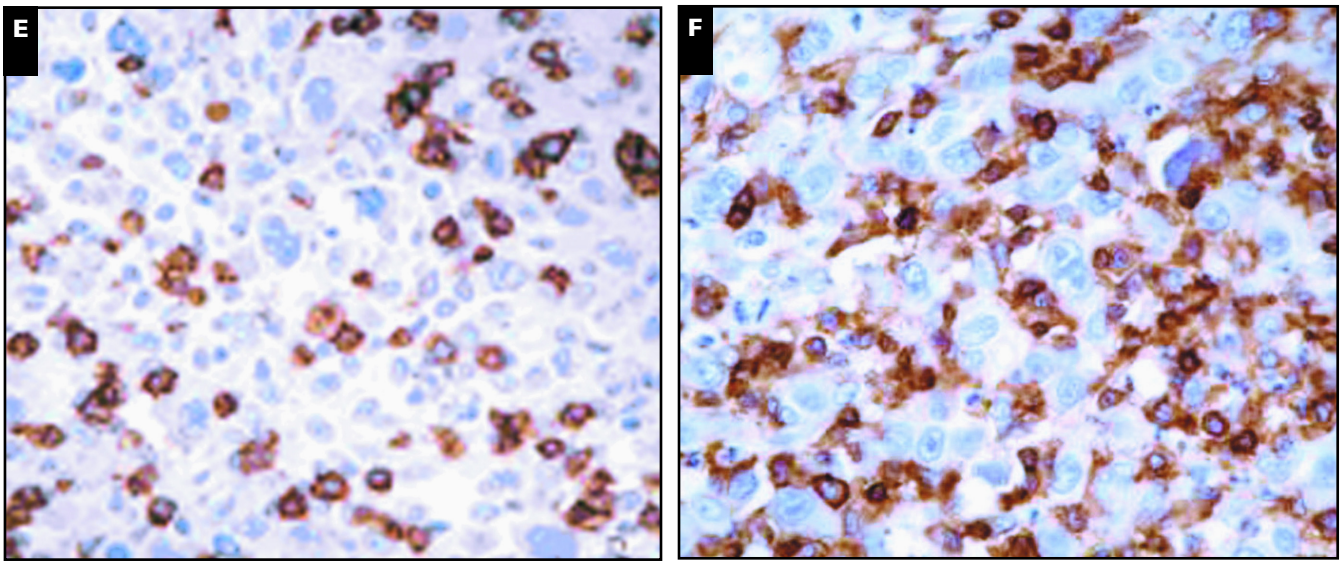

Image 11 In this case CD2, CD43, CD45RO, and clusterin were also expressed, and CD5, CD20, and ALK-1 were negative (not shown). Monoclonal T-cell receptor γ chain gene rearrangements were detected by polymerase chain reaction (not shown). Contributed by P. Aoun.

with classical Hodgkin lymphoma. However, all of these cases expressed T-cell markers and had monoclonal T-cell receptor gene rearrangements. A subset of ALK– ALCLs can be positive for Epstein-Barr virus, with a frequency similar to PTCL and unlike ALK+ ALCL.[19]

Is CD30 Expression Essential for the Diagnosis of ALCL?

During the session, Bharat Nathwani, MD, asked this question to stimulate discussion. As he admitted, this question is more theoretical than practical for the diagnosis of ALK+ ALCL. All cases of ALK+ ALCL submitted to the Workshop were CD30+. Neither we nor Dr Nathwani (verbal communication) have seen a case of ALK+ ALCL that was negative for CD30.

For the diagnosis of ALK– ALCL, this question is perhaps more relevant. Cases of T-cell lymphoma exist that involve lymph node sinuses and are composed of anaplastic cells but do not express CD30. If not for the absence of CD30, these neoplasms would fit, more or less, into the category of ALK– ALCL. These neoplasms are infrequent, but a number of participants in the session mentioned that they had seen such a case. The question asked by Dr Nathwani was not answered, although some participants voiced the opinion that CD30 was a requirement for the diagnosis of ALK– ALCL. This issue is less relevant for the many participants who did not think the term ALK– ALCL should be used.

What Is the Argument for Designating ALK– ALCL as PTCL?

As mentioned, perhaps the best argument is that ALK– ALCL cases do not seem to be distinctive at the immunophenotypic or molecular level.[39] There is other more circumstantial evidence as well. Many studies have shown that the prognosis of patients with ALK– ALCL is worse than that of patients with ALK+ ALCL[8,9,11] and similar to that of patients with PTCL, unspecified.[39] Thus, there seems to be no clinical reason for separating ALK– ALCL from PTCL, unspecified. Second, a subset of patients with ALK– ALCL has a history of another type of T-cell lymphoma. For example, mycosis fungoides, over time, can histologically transform to an anaplastic neoplasm that strongly expresses CD30 and spreads to lymph nodes. Similarly, when cutaneous ALCL clinically progresses, involvement of lymph nodes or other extranodal sites can develop that resembles ALK– ALCL. These scenarios suggest that ALK– ALCL may be an end stage of histologic transformation for other types of T-cell lymphoma.

ALCL Involving Skin

Cutaneous ALCL, which was a major focus of session 5, is a separate category in the WHO classification.[2] These neoplasms seem to be closely related to lymphomatoid papulosis or may represent part of a spectrum that includes lymphomatoid papulosis at one end and cutaneous ALCL at the other.[40]

It is important to remember that approximately 10% to 20% of patients with systemic ALCL can have skin involvement. From the standpoint of differential diagnosis, this is not usually problematic for cases of ALK+ ALCL because ALK expression is extremely rare (or absent) in cutaneous ALCL.

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In contrast, reliable criteria are not currently available to distinguish cutaneous ALCL from systemic ALK– ALCL involving skin. In addition, there are no criteria to predict which cases of cutaneous ALCL are likely to disseminate to lymph nodes and other sites. Three cases submitted to the Workshop highlighted these issues. Case 5 was a patient with skin lesions that histologically resembled cutaneous ALCL or type C lymphomatoid papulosis **Image 12**. The lesions spontaneously resolved in 3 months, consistent with lymphomatoid papulosis. However, staging studies showed widespread systemic disease. Case 209 was a 64-year-old man with skin disease resembling cutaneous ALCL. However, he had rapidly growing disease that required chemotherapy. After a 2-year waxing and waning clinical course, a liver mass developed. Are these 2 cases cutaneous ALCL that disseminated or systemic ALK– ALCL first manifesting in skin?

Case 196 raised different issues. This was a 51-year-old man with a long history of cutaneous plaques. These lesions were mostly dense dermal infiltrates of predominantly small lymphoid cells with scattered larger CD30+ cells, and exocytosis was present in some biopsy specimens. A spindled CD30+ anaplastic tumor then developed in an inguinal lymph node. This case was submitted as an example of cutaneous ALCL with progression to sarcomatoid ALK– ALCL in a lymph node. The consensus panel did not come to a firm diagnosis for this case, although PTCL, unspecified arising in skin and transformation of mycosis fungoides were considered as possible diagnoses.

Summary

ALK+ ALCL has become a relatively well-defined entity at the histologic, immunophenotypic, and molecular levels. The availability of ALK immunostaining has allowed pathologists to recognize the wide histologic spectrum and unusual clinical manifestations of this disease. There is currently no clear consensus regarding ALK– ALCL, although the predominant opinion expressed is that these neoplasms are not a distinct entity at the immunophenotypic or molecular level. Additional markers are needed to predict which cases of cutaneous ALCL will disseminate and to distinguish systemic ALK– ALCL involving skin from cutaneous ALCL

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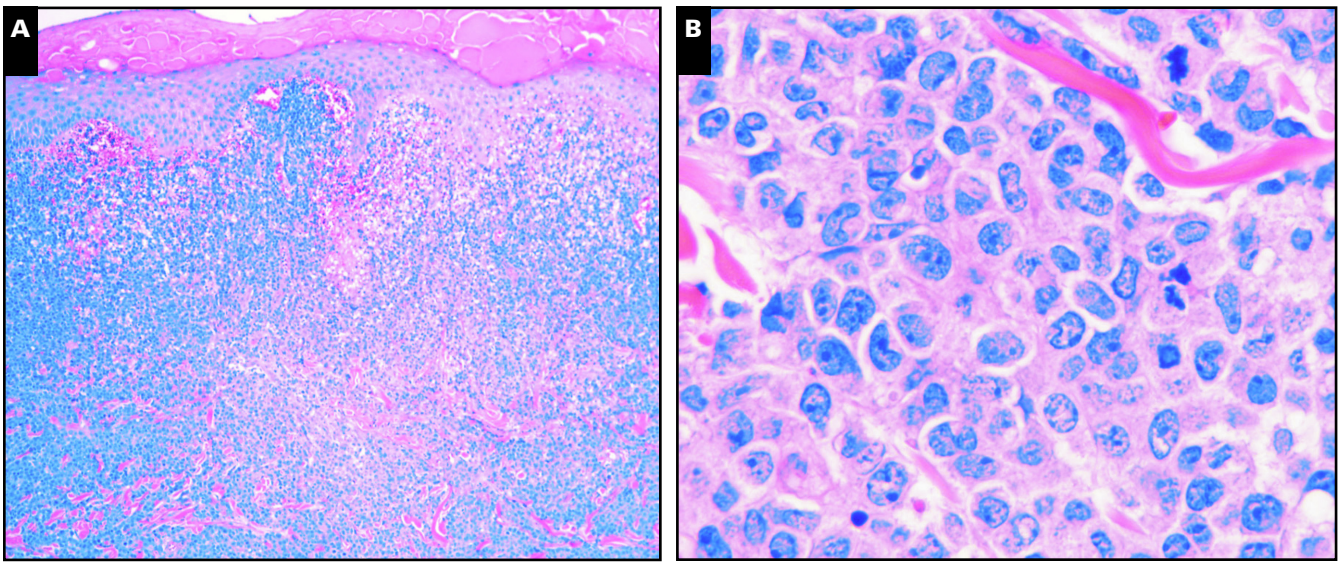

Image 12 (Case 5) Anaplastic lymphoma kinase (ALK)– anaplastic large cell lymphoma involving skin. **A**, The dermis was extensively involved with ulcer (H&E, ×100). **B**, The neoplastic cells were large and anaplastic (H&E, ×400). The skin lesions regressed, consistent with lymphomatoid papulosis type C, but staging studies showed widespread disease. Contributed by C.E. Bueso-Ramos.

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