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Review Article

Anaplastic Lymphoma Kinase-Positive Large B-Cell Lymphoma: A Distinct Clinicopathological Entity

Shiyong Li

Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322, USA

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Abstract: Anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+ LBCL) represents a distinct subtype of mature B-cell neoplasms in the most recent WHO classification of hematolymphoid neoplasms. It has a characteristic immunoblastic/plasmablastic morphology, a distinct immunophenotypic profile and recurrent cytogenetic/molecular genetic abnormalities, and has been reported in both the adult and pediatric populations. With the advent of new ALK inhibitors for possible targeted therapy clinical trials, it is important to recognize this new entity, particularly in the pediatric population because the prognosis is worse than the more common ALK+ anaplastic large cell lymphoma. Though rare, awareness of its existence will avoid potential misdiagnosis and facilitate appropriate management.

Key Words: Anaplastic lymphoma kinase, ALK, diffuse large B-cell lymphoma, t(2;17), *CLTC/ALK*

Introduction

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase of the insulin receptor superfamily. ALK was first discovered as part of the nucleophosmin (NPM)-ALK fusion protein as a result of the t(2;5)(p23;q35) chromosomal translocation frequently seen in anaplastic large cell lymphoma, a subtype of mature T-cell neoplasms [1, 2]. The native ALK is mainly expressed in the developing central and peripheral nervous system, and is normally not expressed in hematopoietic cells [3-5]. Besides ALK-positive anaplastic large cell lymphoma, various solid tumors, including inflammatory myofibroblastic tumor and other soft tissue tumors [6-10], lung cancer [11] and brain tumors [12-16] were found to aberrantly express ALK. The most common mechanism of ALK overexpression is through formation of a fusion protein with a partner due to chromosomal translocations. However, activation through point mutation and gene amplification has also been demonstrated.

ALK was initially believed to be expressed only in anaplastic large cell lymphoma. In 1997, Delsol *et al* reported a small series of diffuse large B-cell lymphoma with expression of ALK (ALK+ LBCL) [17]. To date, approximately 40 cases of ALK+ LBCL have been described in the English literature and those cases share similar morphologic, immunophenotypic and molecular genetic characteristics. In fact, ALK+ LBCL is now considered to be a distinct entity of mature B-cell neoplasms in the new WHO classification of hematolymphoid neoplasm [18]. Most patients with ALK+ LBCL presented with stage III/IV disease and were clinically worse than the more common ALK+ anaplastic large cell lymphoma, particularly in the pediatric population. Therefore, recognition of this rare entity will further our understanding of its pathobiology and development of more efficient treatment including targeted therapy.

Clinical Features

Since the initial description of ALK+ LBCL by Delsol *et al* in 1997 [17], about 40 cases have been described. Their clinical features are summarized in **Table 1**. The youngest patient affected was 9 years old and the oldest one was 71 years old, with a mean age of 44.5 years. Approximately 27% of the cases occurred in the pediatric population (younger than 18 years). There is a male predominance

Table 1 Clinical features of the reported ALK+ LBCL cases

Authors	Case	Age/sex	Sites of disease	Stage	Outcome
Delsol *et al* [17]	1	53/M	Systemic lymph nodes and spleen	IVA	DOD 26 months after CHX and BMT
	2	14/M	N/A	I	Alive without disease 156 months after CHX
	3	37/M	Mediastinal lymph node	II	DOD after CHX
	4	44/M	N/A	III-IV	DOD after CHX
	5	67/M	N/A	III-IV	Lost to followup 11 months after CHX
	6	51/M	N/A	III-IV	Alive without disease 14 months after CHX
	7	60/M	N/A	III-IV	DOD after CHX
Gascoyne *et al* [19]	1	46/M	Supraclavicular and abdominal lymph nodes	III	Alive without disease 27 months after CHX and XRT
	2	45/F	Inguinal lymph node	N/A	N/A
	3	49/M	Systemic lymph nodes and epidural mass	IV	Alive with disease 9 months after CHX and XTR
	4	48/M	Axillary lymph node	IA	Alive without disease 27 months after CHX
	5	58/M	Supraclavicular lymph node	IV	DOD 6 months after CHX
De Paepe *et al* [20]	1	10/M	Cervical mass	II	Alive without disease 6 months after CHX
	2	13/F	Cervical lymph node	III	DOD 3 months after CHX and BMT
	3	26/M	Cervical lymph node	II	Alive without disease 44 months after CHX and BMT
Chikatsu *et al* [21]	1	36/F	Intramuscular and bilateral ovarian masses	IV	DOD 11 months after CHX
Onciu *et al* [22]	1	16/M	Systemic lymph node and multiple lytic skeletal lesions	IV	DOD 24 months after CHX and XTR
	2	10/M	Head and neck lymph nodes	II	Alive without disease 156 months after CHX and XTR
Adam *et al* [23]	1	35/M	Cervical and supraclaviclular lymph nodes	IIA	DOD 14 months after CHX and BMT
McManus *et al* [24]	1	21/M	Pyloric mass	IIE	Alive without disease 2 years after CHX
Colomo *et al* [25]	1	34/M	Systemic lymph nodes	N/A	DOD 8 months after therapy
Ishii *et al* [26]	1	33/M	Right neck lymph node	N/A	DOD 31 months after CHX, XTR and BMT
Rudzki *et al* [27]	1	48/M	Neck mass	IIIB	DOD 3 months after CHX
	2	49/M	Abdominal lymph nodes	IV	Alive on CHX
Gesk *et al* [28]	1	13/M	Cervical lymph node	II	Alive with partial remission on CHX
	2	12/F	Mediastinal and cervical lymph nodes	II	Alive without disease 4 years after CHX
	3	16/M	Systemic lymph nodes	IV	DOD 1 year after CHX and BMT
Isimbaldi *et al* [29]	1	9/F	Left cervical mass	I	DOD 9 months after CHX

Bubala *et al* [30]	1	9/M	Systemic lymph nodes with bony lesions	III	DOD 5 months after CHX
Reichard *et al* [31]	1	41/F	Cervical lymph node	I	Alive without disease 58 months after CHX and local XTR
	2	49/F	Cervical lymph node	I	Alive without disease 36 months after CHX and local XTR
	3	71/M	Nasopharyngeal mass	IV	DOD 22 months after CHX and local XTR
	4	53/M	Cervical lymph node	I	Alive on CHX
Stachurski *et al* [32]	1	33/M	Right neck lymph node	IV	Alive with recurrent disease 10 months after CHX
Lee *et al* [33]	1	26/F	Axillary lymph node	IV	Lost to followup 6 months after CHX
	2	35/M	Axillary lymph node	IV	DOD 18 months after CHX and XTR
	3	24/M	Neck lymph node	IV	DOD 17 months after CHX, BMT and local XTR
Momose *et al* [34]	1	53/M	Left supraclavicular lymph node	IV	Alive with recurrent disease 4 months after CHX
	2	41/M	Abdominal lymph nodes	IIE	Alive with CHX
Personal experience	1	57/M	Inguinal lymph node	IV	DOD 2 years after CHX
	2	14/M	Cervical lymph node	I	Alive without disease 14 months after CHX

CHX, chemotherapy with various cytotoxic and/or cytostatic agents; XTR, radiation therapy; DOD, died of diease; BMT, bone marrow or peripheral blood stem cell transplantation; N/A, not available.

with a male to female ratio of about 3.6:1 (32 vs 9). 23 patients presented with higher stage disease (III and IV) while 15 with lower stage disease (I and II or IIE). Interestingly, in patients younger than 18 years old, more patients presented with lower stage than higher stage diseases, a fact that may be attributed to early diagnosis in the pediatric population.

The most common anatomic site of involvement is cervical lymph node. However, any lymph node can be involved and systemic lymphadenopathy and extranodal presentation is not uncommon. Despite aggressive treatment, approximately half of the patients died of disease 4-26 months after therapy, a prognosis similar to other diffuse large B-cell lymphomas, but worse than the more common ALK-positive anaplastic large cells lymphoma [35, 36]. The outcome is not much different in patients younger than 18 with relatively early stage disease at diagnosis (**Table 1**).

Histopathology

The lymph node architecture in almost all cases is partially or completely effaced by a diffuse proliferation of large neoplastic lymphoid cells (**Figure 1**). Focal sinusoidal infiltration, coagulative necrosis and starry-sky pattern may be present [17, 31]. Cases with a prominent intravascular component has also been described [31].

Cytologically, the lymphoma cells in all reported cases exhibit either an immunoblastic or plasmablastic morphology with a round, centrally or eccentrally located nucleus, a prominent central nucleolus and a moderate amount of eosinophilic or amphophilic cytoplasm (**Figure 1**). Occasional binucleated or multinucleated cells mimicking Reed-Sternberg cells may also be seen [31]. In extranodal sites, the lymphoma cells in ALK+ LBCL cells may form cohesive sheets resembling nonhematolymphoid neoplasms [21, 24].

Immunophenotype

Extensive immunophenotypic profiling of ALK+ LBCL by flow cytometry has been unsuccessful due to the cohesiveness and immunoblastic/plasmablastic morphology of the lymphoma cells. Among the reported

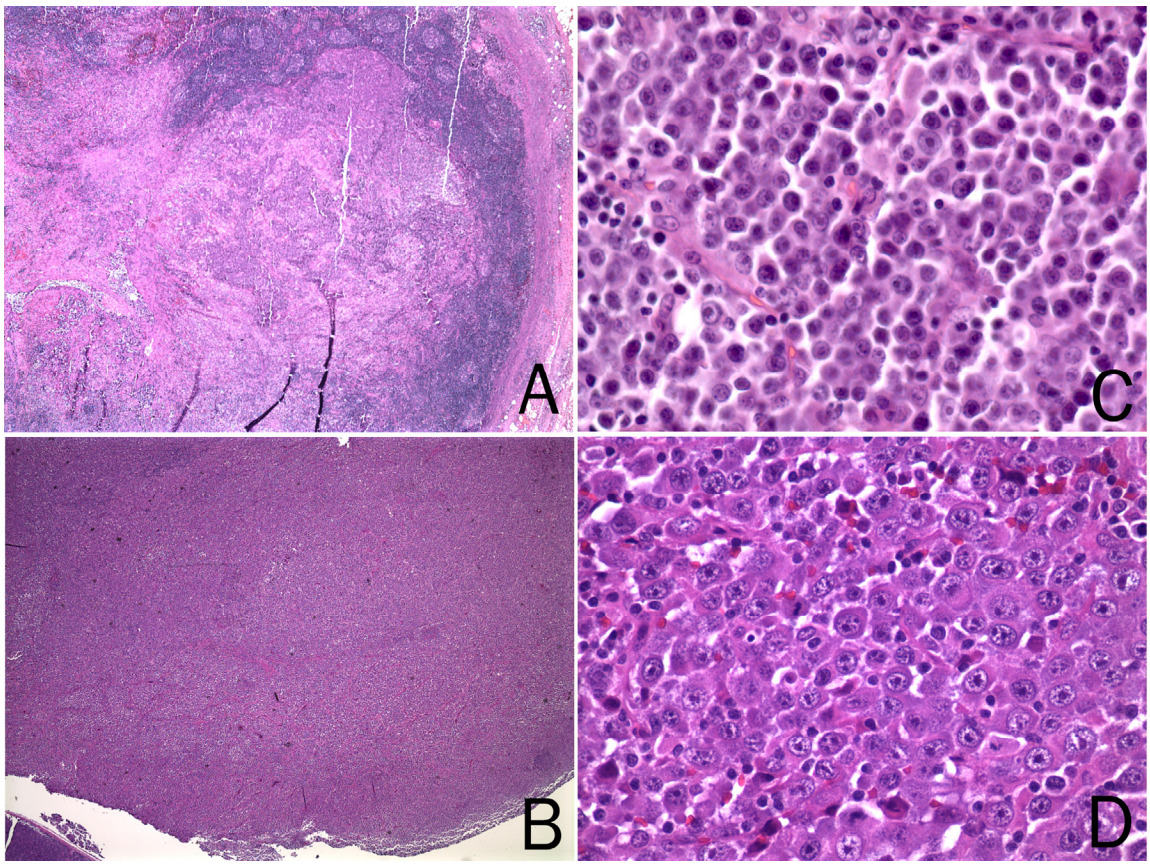

Figure 1 Partial architectural effacement of the inguinal lymph node from a 57 year old male by ALK+ LBCL with an immunoblastic morphology (H&E staining. **A**, 4x; **B**, 40x). Another ALK+LBCL from a 14 year old male with diffuse architectural effacement and a plasmablastic morphology (H&E staining. **C**. 4x; **D**, 40x).

cases, only one had a flow cytometric immunophenotyping analysis performed successfully [31]. The lymphoma cells in this case demonstrated increased side angle light scatter properties, and expressed CD45, CD4, HLA-DR and moderate density CD38. As expected, they were negative for mature B cells markers including CD19, CD20, CD23, FMC7 and surface immunoglobulin light chains. They also failed to express T cell (CD2, CD3, CD5, CD7 and CD8), myelomonocytic (CD14 and CD33) lineage markers as well as CD10.

Immunohistochemical staining with a panel of antibodies has been the mainstay to characterize the neoplastic cells of ALK+ LBCL (**Figures 2** and **3**). As summarized in **Table 2**, the lymphoma cells are uniformly positive for CD138/VS38c, MUM1 and epithelial membrane antigen (EMA). Most of them demonstrate intracellular immunoglobulin light chain restriction and show a preferential usage of IgA over IgG (18 vs 3). They have lost the B cell lineage-specific markers CD19, CD20, CD22 and CD79a with only focal and weak expression of these markers in few cases, suggesting terminal plasma cell differentiation. Interestingly, CD4 expression was observed in three quarter and CD57 in about one third of the cases examined. The expression of other T cell, natural killer cell and myelomonocytic cell lineage markers, including CD56 and CD68, was absent. There was no evidence of EBV infection.

In contrast to ALK-positive anaplastic large cell lymphoma, CD30 expression is essentially absent. Though a few cases were reportedly positive for CD30, the expression was either focal or weak. Expression of CD45 is absent in about a quarter of the cases reported. In light of its cytomorphology, uniform expression of EMA and, in rare cases, focal expression of cytokeratins, ALK+ LBCL may occasionally be confused with metastatic carcinoma.

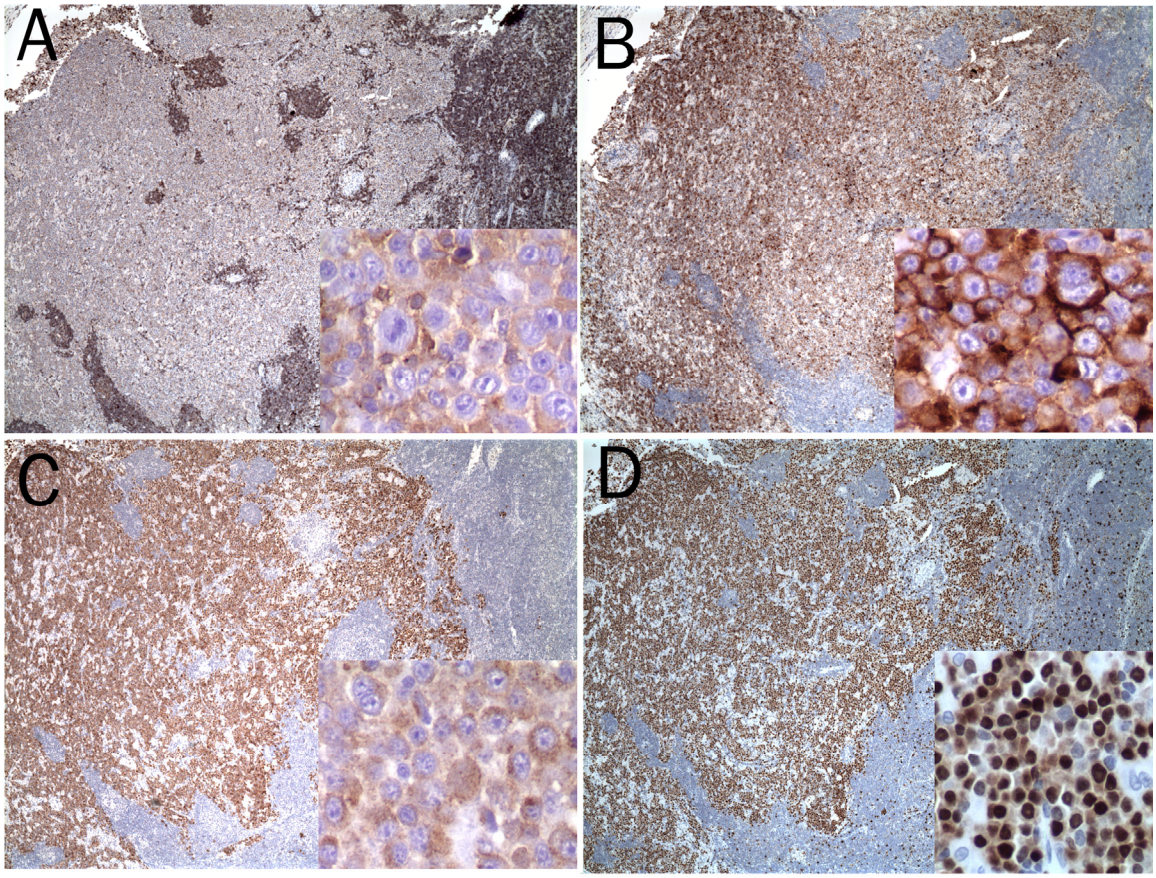

Figure 2 Immunohistochemical stains showing the lymphoma cells to be weakly positive for CD45 (**A**), strongly positive for CD138 (**B**), ALK (**C**) and MUM1 (**D**) (4x and 40x for insets).

As the name implies, the neoplastic cells in all cases of ALK+ LBCL strongly express ALK (**Figure 2C**). The majority of them have a granular cytoplasmic staining pattern with rare exceptions, which demonstrate cytoplasmic and nuclear staining [19, 22, 33].

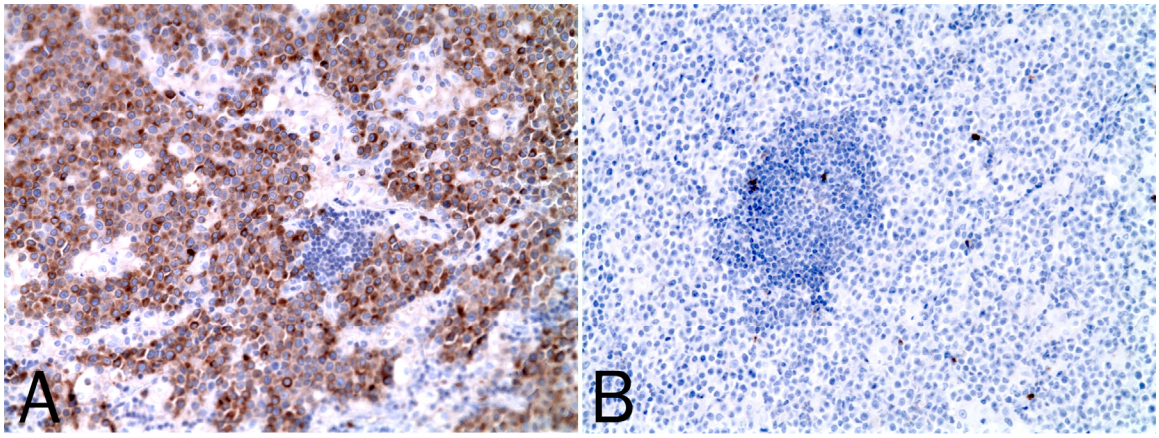

Figure 3 Immunohistochemical stains for kappa (**A**) and lambda (**B**) immunoglobulin light chains showing the lymphoma cells to be kappa light chain-restricted (20x).

Table 2 Immunophenotypic profile of the reported ALK+ LBCL cases

Antibody	Number of positive cases/total (%)	Staining pattern
CD20	2/41 (5)	Focal and weak
CD22	0/3	
CD79a	6/40 (15)	Focal and weak
CD19	1/3 (33)	Membrane
CD138/VS38c	41/41 (100)	Strong and cytoplasmic
CD38	5/7 (71)	Membrane and cytoplasmic
PAX5	2/8 (25)	Focal nuclear
MUM1	8/8 (100)	Strong nuclear
EMA	39/39 (100)	Strong membrane/cytoplasmic
KAPPA/LAMBDA	29/38 (76)	Strong cytoplasmic
IGA/G	21/30 (70)	Strong cytoplasmic
CD45	15/21 (71)	Focal and weak
CD30	4/41 (10)	Focal
ALK	41/41 (100)	Cytoplasmic granular (majority)
CD3	0/41 (0)	
CD4	17/23 (74)	Focal and weak
CD5	0/38 (0)	
CD57	8/21 (38)	Focal
CD43	4/15 (27)	Focal
CD56	0/8 (0)	
TIA1	0/6 (0)	
Perforin	1/2 (50)	Strong cytoplasmic
KI-67	4/4	50-90%
AE1/AE3	1/5 (20)	Focal
BCL2	0/5 (0)	
EBV	0/13 (0)	

Table 3 Cytogenetic and molecular features of the reported ALK+ LBCL cases

Authors	Case studied/total	Cytogenetics	Molecular genetics
Delsol *et al* [17]	3/7	N	ND
Gascoyne *et al* [19]	5/5	t(2;17;7)(p23;q23;q?22)	*CLTC-ALK* by FISH
De Paepe *et al* [20]	3/3	t(2;17)(p23;q23)	*CLTC-ALK* by FISH
Chikatsu *et al* [21]	1/1	t(2;17)(p23;q23)	*CLTC-ALK* by RT-PCR
Onciu *et al* [22]	2/2	t(2;5)(p23;q35)	*NPM-ALK* by RT-PCR
Adam *et al* [23]	1/1	t(2;5)(p23;q35)	*NPM-ALK* by RT-PCR
McManus *et al* [24]	1/1	N/A	*CLTC-ALK* by RT-PCR
Colomo *et al* [37]	0/1	N/A	N/A
Ishii *et al* [26]	0/1	N/A	N/A
Rudzki *et al* [27]	1/2	N/A	*NPM-ALK* by RT-PCR
Gesk *et al* [28]	3/3	N/A	*CLTC-ALK* by FISH
Isimbaldi *et al* [29]	1/1	N/A	*CLTC-ALK* by RT-PCR
Bubala *et al* [30]	1/1	N/A	*CLTC-ALK* by FISH
Reichard *et al* [31]	1/4	N/A	*CLTC-ALK* by FISH
Stachurski *et al* [32]	1/1	t(2;17)(p23;q23)	*CLTC-ALK* by FISH
Lee *et al* [33]	3/3	N/A	*CLTC-ALK* by FISH
Momose *et al* [34]	2/2	N/A	*CLTC-ALK* by RT-PCR
Personal experience	1/2	t(2;17)(p23;q23)	*CLTC-ALK* by FISH

FISH, fluorescence in situ hybridization; RT-PCR, reverse transcription polymerase chain reaction; ALK, anaplastic lymphoma kinase; CLTC, clathrin; N/A, not available; N, negative for translocation involving ALK by karyotyping; ND, No *NPM-ALK* by RT-PCR

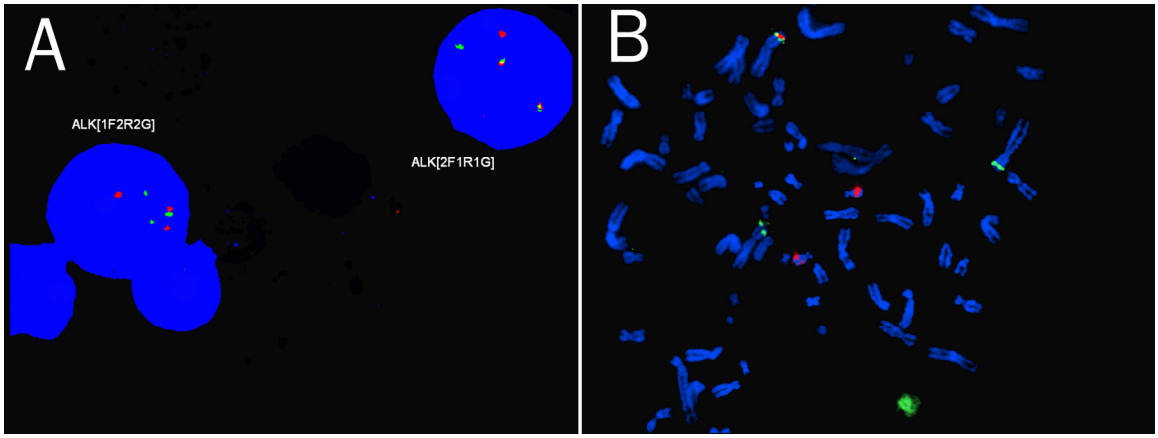

Figure 4 Fluorescent in situ hybridization of interphase (**A**) and metaphase (**B**) nuclei using *ALK* breakapart probe (LSI Alk, Vysis/Abbott, Downers Grove, USA) demonstrating the reciprocal translocation of t(2;17) involving *ALK* on chromosome 2 and presumably *CLTC* on chromosome 17.

Molecular Genetics

Initial studies by Delsol *et al* failed to demonstrate the presence of *NPM-ALK* by RT-PCR in 3 of 7 ALK+ LBCL cases studied [17]. Subsequent reports have shown that the majority of ALK+ LBCL cases contain *CLTC-ALK* fusion gene secondary to t(2;17) translocation as demonstrated by either conventional karyotyping, FISH or RT-PCR (**Table 3**). It is possible that the cases originally reported by Delsol *et al* may instead harbor the t(2;17) and RT-PCR designed specifically for *NPM-ALK* fusion gene may have failed to detect *CLTC-ALK*. A small subset of ALK-positive anaplastic large cell lymphoma and inflammatory myofibroblastic tumor also harbor the t(2;17) translocation and aberrantly overexpress ALK [38-41], suggesting a broader role of CLTC-ALK fusion protein in tumorigenesis.

The *ALK* gene is located on chromosome 2p23. It is normally expressed in the developing central nervous system, but not in hematopoietic cells [3-5]. Aberrant expression of ALK has been demonstrated in ALK-positive anaplastic large cell lymphoma via chromosomal translocations, causing fusion of ALK with a variety of partners [42]. The most common translocation is t(2;5)(p23;q25), resulting in a 80 kd fusion NPM-ALK [1]. It occurs in about 75% of anaplastic large cell lymphoma. Other translocations include t(1;2)(q25;q23)[*TPM3-ALK*], t(2;3)(p23;q21)[*TGF-ALK*], inv2(p23;q35)[*ATIC-ALK*], t(2;X)(p23;q11-12)[*MSN-ALK*], t(2;19)(p23;q13)[*TPM4-ALK*], t(2;17)(p23;q25)[*ALO17-ALK*] and t(2;22)(*p23;q11.2*)[*MYH9-ALK*].

Abnormal expression of ALK has also been observed in solid tumors [6-16]. Soda *et al* first demonstrated inv(2)(p21;p23) in a subset of non-small cell carcinoma of lung, resulting in formation EML4-ALK fusion protein [11, 43]. More recently, several groups have identified *ALK* gene mutation and amplification in familiar as well as sporadic neuroblastomas [12, 13, 15, 16]. *NPM-ALK* transgenic mice developed both B and T cell lymphomas [44-48]. These findings suggest an important role of ALK activation in the pathogenesis of malignant lymphoma and solid tumors.

The physiological target(s) or substrate(s) of ALK remains elusive. Much of the studies have been focusing on the fusion protein NPM-ALK with constitutive tyrosine kinase activity [42, 49]. NPM-ALK has been shown to interact with numerous intracellular targets involved in signal transduction pathways important for cell proliferation, cell cycle progression and apoptosis [42, 44, 50]. These include the JAK/STAT pathway, m-TOR pathway as well as the SHIP2 tyrosine phosphatase negative regulatory loop. More recently, NPM-ALK has been shown to upregulate the expression of an immunosuppressive molecule on the cell surface, CD274 [51], suggesting a role in tumor evasion of the human immune surveillance. Little is known about the targets of CLTC-ALK fusion protein. Momose *et al* [34] demonstrated hyperactivation of STAT3 in ALK+ LBCL compared to ALK- LBCL,

suggesting that the CLTC-ALK fusion protein may also act through the JAK/STAT pathway to induce malignant transformation.

Differential Diagnosis

The characteristic morphologic and immunophenotypic profiles should allow for distinction of ALK+ LBCL from other entities including anaplastic large cell lymphoma, plasmablastic myeloma, metastatic carcinoma and other morphologic variants of diffuse large B-cell lymphoma (immunoblastic, plasmablastic and anaplastic). Anaplastic large cell lymphoma is usually strongly positive for CD30 with a T-cell phenotype, negative for plasma cell markers CD138, MUM1 and intracellular monoclonal immunoglobulin light or heavy chain proteins, and frequently demonstrates molecular evidence of clonal T-cell receptor gene rearrangement. Plasmablastic myeloma has not been reported to express ALK, and would be associated with other myeloma features such as lytic bone lesions and serum or urine paraproteins. Plasmablastic lymphoma has an immunophenotype similar to ALK+ LBCL, but they tend to occur in the oral cavity of patient with HIV infection. They are usually EBV-positive and always ALK-negative. Anaplastaic variant of diffuse large B-cell lymphoma can be easily distinguished from ALK+ LBCL because B-cell lineage specific markers such as CD20 and CD79 are strongly positive, and ALK is always negative. Occasionally, metastatinc carcinoma may enter the differential diagnosis because focal cytokeratin staining has been seen in rare ALK+ LBCL cases. However, evidence of plasma cell differentiation with light chain or heavy chain restriction distinguishes ALK+ LBCL from metastatic carcinoma.

In conclusion, ALK+ LBLC is a rare subtype of diffuse large B-cell lymphoma with a characteristic histomorphology, immunophenotypic profile, recurrent cytogenetic abnormality and dismal prognosis. It should be distinguished from other subtypes of diffuse large B-cell lymphoma, ALK-positive anaplastic large cell lymphoma, plasmablastic myeloma, and nonhematolymphoid neoplasms using a panel of antibodies and molecular techniques if needed. Recent *in vitro* and animal studies have shown promise of immunotherapy using ALK as a vaccine or targeted therapy with small molecule inhibitors of ALK [52-55], providing potential new treatment modalities for ALK+ LBCL.

Please address all correspondences to Shiyong Li, M.D., Ph.D., Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322. Tel: 404-712-4140; Fax: 404-712-0819; Email: sli2@emory.edu.

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