Modern Pathology (2007) 20, 310–319

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ALK-positive diffuse large B-cell lymphoma: report of four cases and review of the literature

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We report detailed clinical and pathologic features of four cases of anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma (ALK-DLBCL), a rare entity with only 29 currently reported cases. This study is the third largest of all reported series. Biopsies from four adult patients aged 41, 49, 53, and 71 years (three lymph nodes and one nasopharyngeal mass) exhibited immunoblastic/plasmablastic morphology. By immunohistochemistry and/or flow cytometry, they expressed cytoplasmic ALK-1, CD138, VS38 (3/3), monoclonal cytoplasmic light chain, CD45, EMA, CD4, and CD57 (2/3), and were negative for CD3, CD30, CD56, and TIA-1. Two showed variable CD79a expression, and one had rare CD20(+) cells. Two of three cases exhibited rare CD43(+) reactivity. One case showed scattered cytokeratin(+) cells, which could possibly lead to a misdiagnosis of carcinoma. After CHOP and radiotherapy, two stage I patients were free of disease at 58 and 36 months, whereas a stage IV patient was dead of disease at 22 months.
Modern Pathology (2007) **20,** 310–319. doi:10.1038/modpathol.3800742; published online 2 February 2007

Keywords: *ALK*; DLBCL; *NPM/ALK*; *CLTC/ALK*; t(2;17); t(2;5)

In 1997, seven cases of a new subtype of diffuse large B-cell lymphoma expressing the anaplastic lymphoma kinase gene product (ALK-DLBCL) were reported by Delsol *et al*.[1] This lymphoma was identified due to its characteristic lack of CD30 expression in an otherwise large series of classical T-/null cell ALK-positive anaplastic large cell lymphomas (ALCL).[1] ALK-DLBCL exhibits an immunoblastic/plasmablastic morphology, often an intrasinusoidal growth pattern, and is derived from B cells based on expression of monotypic light chain. It shows an unique immunophenotypic profile characterized by a lack of B (CD20, CD79a)- and T-lineage (CD3) markers and CD30, but expression of VS38 and CD138 (plasmacytic markers), variable expression of CD4 and CD57, and cytoplasmic, granular ALK reactivity.

Initially, molecular and protein analyses failed to reveal an *ALK* gene rearrangement.[1] Recently however, *Clathrin/ALK* (*CLTC/ALK*) and *NPM/ALK* gene rearrangements have been identified in 16 and three cases of ALK-DLBCL, respectively.[2–13] All of these cases display the morphologic and immunophenotypic features of ALK-DLBCL, as originally described by Delsol *et al*. Importantly, ALK positivity and *ALK* gene rearrangements can be seen in B-cell lymphomas and are now no longer uniquely restricted to the T-cell lymphoma, ALCL.

To our knowledge, only 29 cases of ALK-DLBCL have been reported thus far in the literature. Herein, we report detailed clinical and pathologic features of four new adult cases of this rare entity.

Materials and methods

Four total cases of ALK-positive DLBCL were identified: three from the hematology consultation files at the University of Texas Southwestern Medical Center from 1997 to 2002 and one from University of New Mexico, 2006. One case was originally diagnosed as an anaplastic plasmacytoma, but was subsequently reclassified. Clinical and laboratory information for each of the four patients was obtained through physician interview. The mean disease-free survival for low stage patients (alive with disease) and the overall median survival for high stage patients (dead of disease) were calculated from the data reported in the literature.

Routine hematoxylin and eosin-stained sections were prepared from formalin-fixed and/or B5-fixed

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Received 12 October 2006; revised 21 November 2006; accepted 27 November 2006; published online 2 February 2007

paraffin blocks. Immunohistochemical analysis included a broad panel of antibodies (Table 1). Fresh tissue from case 2 was submitted for flow cytometric analysis. The cell preparation and data analysis were performed as previously described.[14]

Fluorescence *in situ* hybridization (FISH) for the *Clathrin/ALK* fusion associated with t(2;17)(p23;q23) was performed on case 3 as previously described.[2] FISH evaluation for an *ALK* gene rearrangement using the *ALK* break apart probe from Vysis, Inc. (Downers Grove, IL, USA) was performed on case 4 on a paraffin-embedded tissue section.

Genetic studies could not be attempted on the other two cases owing to lack of available remaining specimen.

Results

Case Reports

A summary of the clinical features of the four patients is provided in Table 2. All patients were adults; two female and two male.

Table 1 Antibodies used for immunohistochemical analysis

Antibody	*Dilution*	*Source*
CD45	1:20	Signet Laboratories, Dedham, MA, USA
CD3	1:200	Dako, Carpinteria, CA, USA
CD20	1:40	Signet Laboratories
CD43	1:320	ImmunoTech, Miami, FL, USA
CD30	1:20	Dako
MIB-1	1:100	Dako
EMA	1:200	Dako
CD57 (Leu-7)	1:10	Becton Dickinson, Franklin Lakes, NJ, USA
CD56	1:20	Monosan, San Francisco, CA, USA
Kappa, poly	1:300	Signet Laboratories
Lambda, poly	1:400	Signet Laboratories
AE1/AE3	1:800	Signet Laboratories
CD79a	1:80	Dako
CD4	1:80	Novocastra, Burlingame, CA, USA
CD138	1:50	Novocastra
TIA-1	1:100	ImmunoTech
ALK-1	1:10	Dako
IgA	1:5000	Dako
CD38	1:10	Serotec, Raleigh, NC, USA
VS38c	1:10	Serotec

Case 1
A 41-year-old female presented with left cervical lymphadenopathy ($2.8 \times 1.8 \times 1.0$ cm). Hematologic studies, lactate dehydrogenase, and serum protein electrophoresis were all within normal limits. A computed tomography (CT) scan of the thorax and abdomen showed no mass lesions or additional lymphadenopathy. An excisional biopsy of the lymph node was performed. A staging bone marrow was negative for involvement by lymphoma. The patient underwent six cycles of CHOP followed by left neck irradiation for stage 1 disease. Follow-up imaging studies show no evidence of lymphoma. At 58 months, she was alive without disease.

Case 2
A 49-year-old female presented with an enlarged left cervical lymph node that she had noticed for about 1 month. She was otherwise asymptomatic and had no significant past medical history. Hematologic and liver function studies were within normal limits. A CT scan of the neck revealed left submandibular lymphadenopathy. CT scans of the head, chest, pelvis, and abdomen were unremarkable. Biopsy of the left cervical lymph node was performed. Staging bone marrow was negative for involvement by lymphoma. She received four cycles of CHOP followed by involved field irradiation for stage 1 disease. At 36 months, she was alive and free of disease.

Case 3
A 71-year-old male presented with a chief complaint of hemoptysis for six weeks. Physical exam revealed a large nasopharyngeal mass (approximately 5.5 cm) without peripheral lymphadenopathy. CBC showed mild normochromic, normocytic anemia. CT scan demonstrated abdominal and retroperitoneal lymphadenopathy. A biopsy of the nasopharyngeal mass was performed. A staging bone marrow showed low level involvement by chronic lymphocytic leukemia, but no evidence of large cell lymphoma. The patient received CHOP and nasopharyngeal irradiation for stage IV disease. Follow-up imaging

Table 2 Clinical features of four cases of ALK-DLBCL

Case no.	*Sex/age (years)*	*Tissue sampled*	*Staging bone marrow*	*Stage of disease*	*Therapy*	*Present clinical status*
1	F/41	Cervical lymph node	Negative	I	CHOP and left neck XRT	Alive without disease at 58 months
2	F/49	Cervical lymph node	Negative	I	CHOP and left neck XRT	Alive without disease at 36 months
3	M/71	Nasopharyn-geal mass	Negative	IV	CHOP and nasopharyn-geal XRT	Dead of disease after 22 months
4	M/53	Left cervical lymph node	Negative	I		Recent case

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; XRT, radiation therapy.

at 6 months revealed residual pelvic disease. Twenty-two months from diagnosis, the patient died of disease.

Case 4
A 53-year-old male presented in Mexico with a rapidly enlarging left neck mass. A biopsy of the mass was performed in Mexico. The patient subsequently sought medical attention in the Southwestern United States. By physical examination and radiologic studies, no additional sites of disease are currently identified. A bone marrow biopsy was negative.

Morphology

All four cases show similar morphologic features (Figures 1 and 2). All cases showed diffuse effacement of the normal architecture by sheets of tumor cells. Sinusoidal infiltration was seen in case 2 (Figure 1a) along with focal coagulative necrosis. Case 1 exhibited prominent, ectatic, blood-filled vascular spaces. Case 3 exhibited a 'starry-sky' pattern. Case 4 shows a prominent intravascular component. The neoplastic cells in all cases were large with round, regular, centrally located nuclei, dispersed chromatin, a single, central, prominent nucleolus, and moderate eosinophilic or amphophilic cytoplasm. Occasional binucleate or rare multinucleate cells resembling Reed–Sternberg cells were seen.

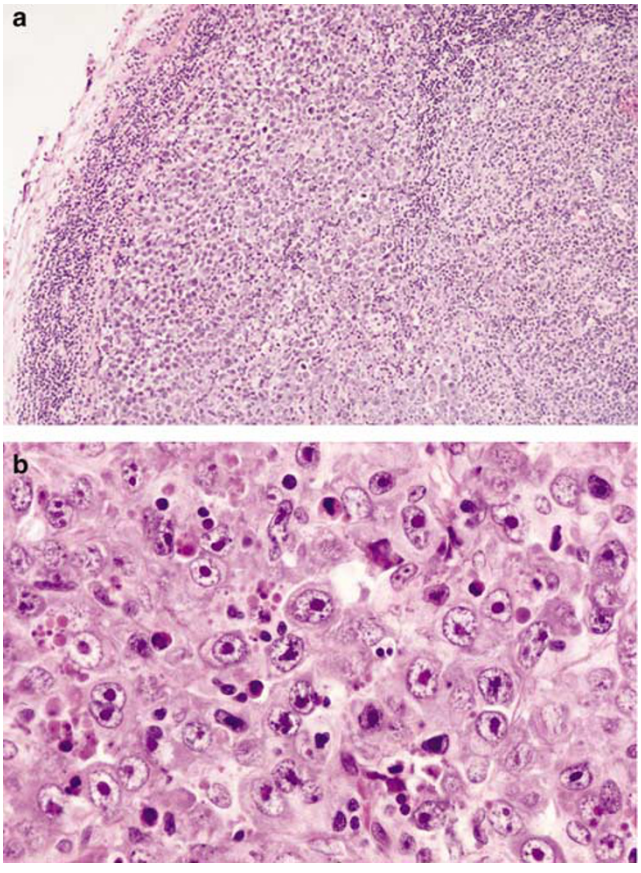

Figure 1 Architectural and cytologic features of ALK-DLBCL. Diffuse proliferation of large cells with round, regular nuclei; single, central, eosinophilic nucleoli, dispersed chromatin, and moderate amounts of eosinophilic cytoplasm. (**a**) Sinusoidal infiltration pattern, (**b**) morphology (case 2, H&E, ×40 and ×500 magnification, respectively).

Immunohistochemistry

Table 3 provides a summary of the immunohistochemical results in our four cases. All tested cases were positive for CD138, monotypic cytoplasmic light chain and CD4 (Figure 3), CD45, EMA, VS38 and were negative for CD3, CD30, CD56, and TIA-1. Each case was positive for ALK in a granular cytoplasmic distribution (Figure 3). Three cases were CD20(−), while case 1 exhibited rare positive cells (Figure 4). Variable and scattered CD79a reactivity was seen in two cases. Two cases showed patchy CD57 positivity (Figure 4) and two cases exhibited rare CD43-positive cells. Occasional cytokeratin (AE1/AE3)(+) cells were seen in one case (Figure 4). OCT2, BOB.1, and MUM-1 were positive in case 4, and PAX-5

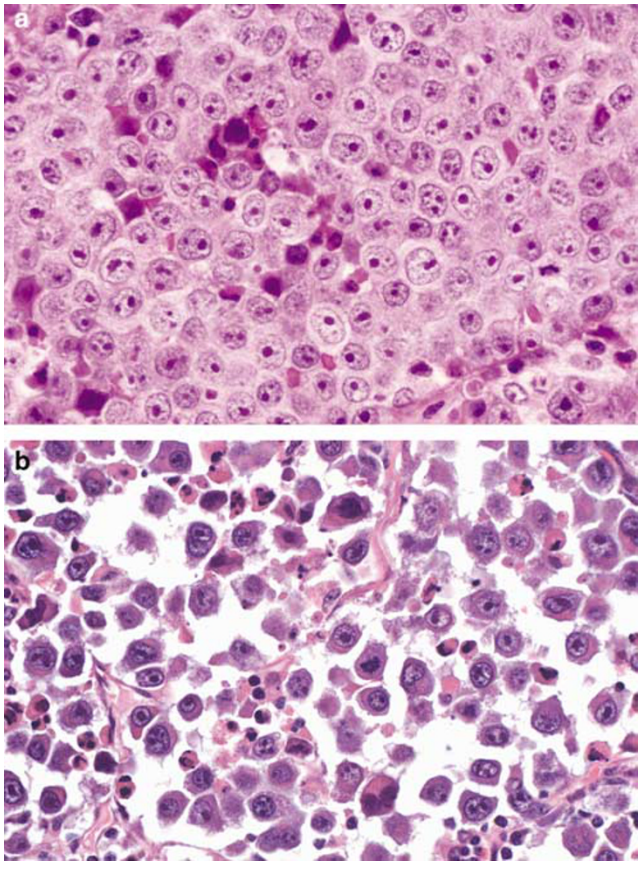

Figure 2 Cytologic features of ALK-DLBCL. (**a**) Case 3, (**b**) case 4 (H&E).

Table 3 Immunophenotypic profile of four cases of ALK-DLBCL

Antibody	*Case 1*	*Case 2*	*Case 3*	*Case 4*
CD20	Rare +	Neg	Neg	Neg
CD79a	Variably +	Neg	Scattered +	Neg
CD138	+	+	+	+
VS38	+	+	+	ND
EMA	Variably +	+	Scattered +	+
Kappa, poly	+	Neg	Neg	Neg (ISH)
Lambda, poly	Neg	+	+	+ (ISH)
CD30	Neg	Neg	Neg	Neg
ALK-1	+	+	+	+
CD4	Patchy +	+ (FC)	Patchy +	Weak +
CD3	Neg	Neg	Neg	Neg
CD45	Variably +	+ (FC)	+	+
CD57	Neg	Patchy +	Patchy +	ND
CD38	Neg	+ (FC)	Neg	Neg
IgA	Equivocal	Equivocal	Equivocal	ND
CD43	Rare +	Rare +	Neg	Rare +
CD56	Neg	Neg	Neg	ND
TIA-1	Neg	Neg	Neg	Neg
Ki-67	50%	50%	80%	50%
Cytokeratin (AE1/AE3)	Neg	Scattered +	Neg	Neg

FC, flow cytometry; Neg, negative; +, positive; ND, not done.

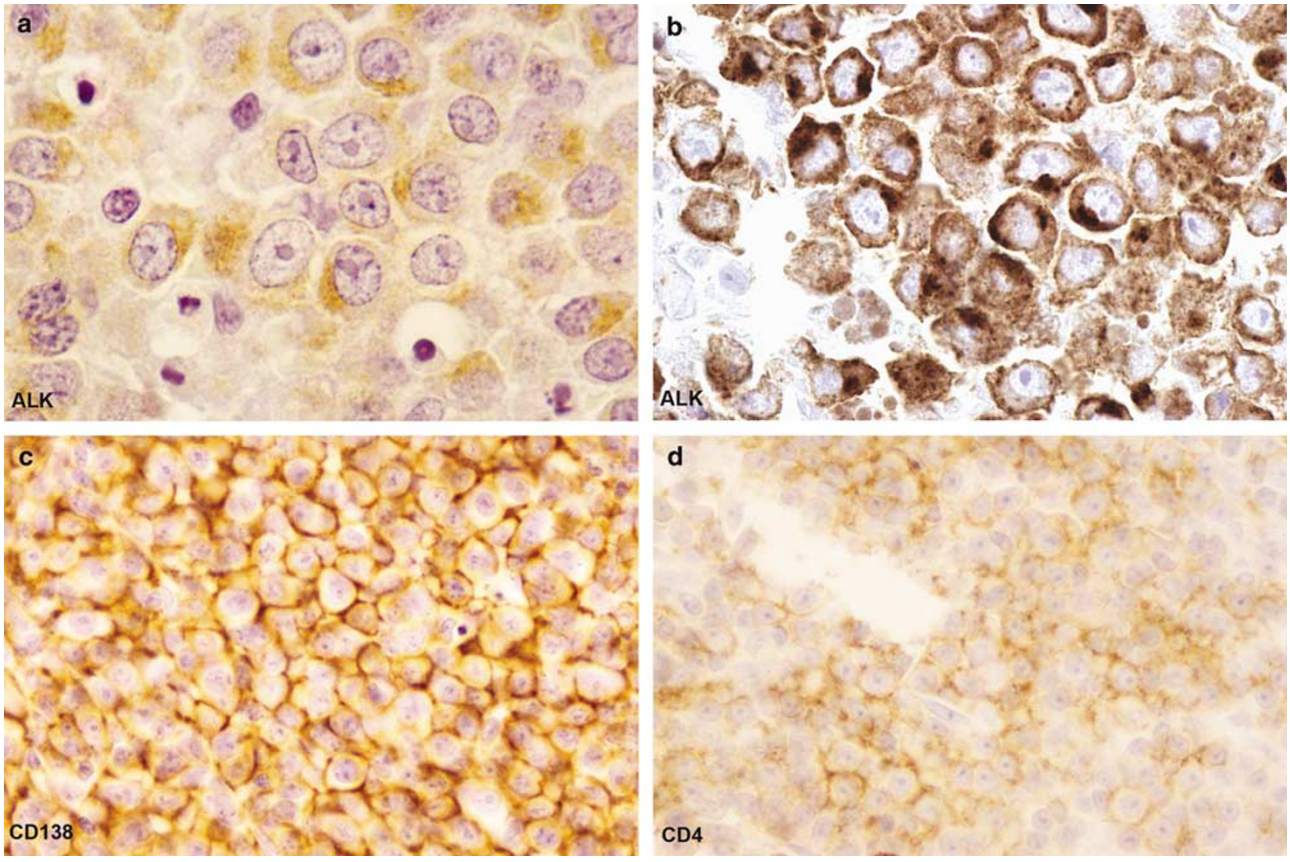

Figure 3 Typical immunohistochemical findings in ALK-DLBCL. Tumor cells are positive for (**a, b**) cytoplasmic, granular ALK, (**c**) CD138, (**d**) CD4 (cases 1, 4, 1, and 1, respectively).

negative. CD38 was negative by immunohistochemistry in three cases, but positive by flow cytometry in one. IgA staining was equivocal in three cases. Cases 1, 2, 3, and 4 exhibited 50, 50, 80, and 50% proliferation indices by Ki-67 staining, respectively.

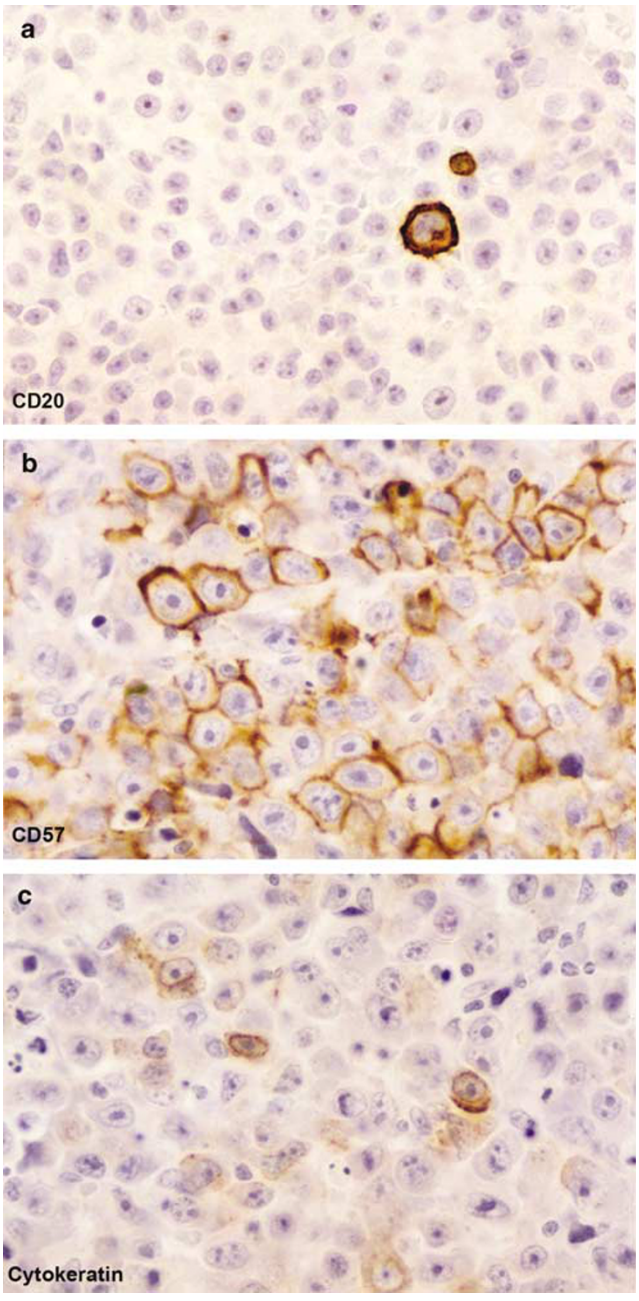

Figure 4 Unusual immunohistochemical findings in occasional cases of ALK-DLBCL. (**a**) Rare CD20-positive tumor cells. (**b**) Scattered and variable CD57 membrane positivity. (**c**) Occasional cytokeratin-positive cells (cases 1, 2, and 2, respectively).

Flow Cytometry

Four-color flow cytometric analysis performed on tissue from case 2 revealed a 1% population of medium to large size cells (based on forward and side angle light scatter properties) expressing CD45, CD4, CD38 (moderate), and HLA-DR (Figure 5). The tumor cells were negative for CD2, CD3, CD5, CD7, CD8, CD10, CD14, CD19, CD20, CD23, FMC7, CD33, and surface kappa and lambda light chains.

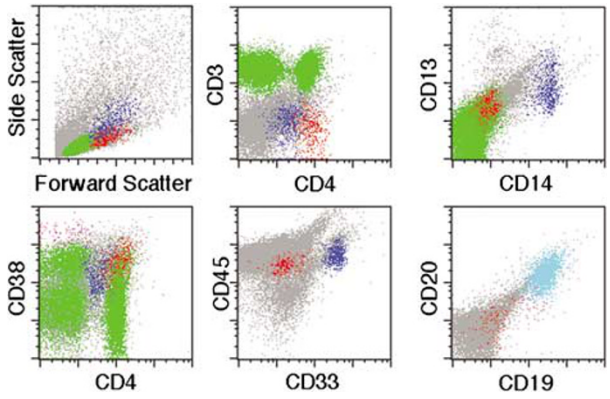

Figure 5 Flow cytometric findings of ALK-DLBCL. A 1% population of medium to large cells (colored in red) expressing CD45, CD4, CD38 (moderate), and HLA-DR is identified (case 2). The tumor cells were negative for CD2, CD3, CD5, CD7, CD8, CD10, CD14, CD19, CD20, CD23, FMC7, CD33, and surface kappa and lambda light chains. Green—T cells; dark blue—monocytes; light blue—small, polytypic B cells; violet—plasma cells.

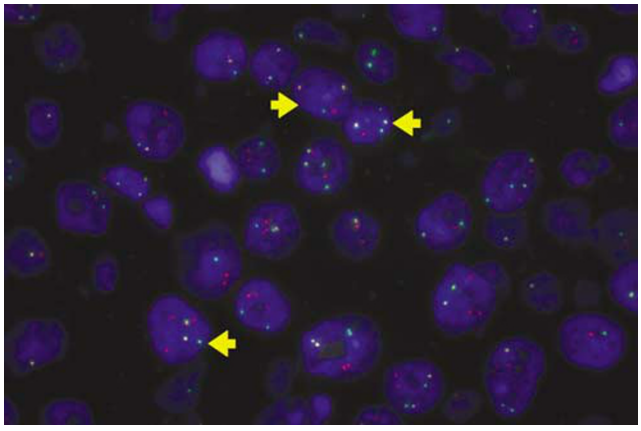

Figure 6 Fluorescence *in situ* hybridization (FISH) of ALK-DLBCL showing *ALK* gene rearrangement using the ALK break apart probe from Vysis, Inc. The FISH pattern is positive for a rearrangement involving the *ALK* gene locus (arrows). The typical abnormal pattern would be expected to show 1R1G1F (one red and one green signal (abnormal) and one fused (yellow) (the remaining normal allele)). In this particular case, the majority of neoplastic cells also demonstrate an additional fused (yellow), signal indicating either a duplication of the *ALK* gene region or an additional copy of chromosome 2.

FISH for ALK Gene Rearrangement

FISH demonstrated an *ALK* gene rearrangement in case 4. Figure 6 demonstrates a clearly separated orange and green signal indicating a rearrangement of the *ALK* gene (arrows). The normal ALK gene signal is seen as overlapping/fusion of the orange and green signals (yellow). As the *ALK* probe is a break apart probe, the translocation partner remains unknown (eg *Clathrin (CLTC)* or *NPM*, etc.). However, given the cytoplasmic granular staining pattern with ALK immunohistochemistry, it is most likely that the partner is *CLTC*. FISH analysis on case 3

technically failed owing to lack of detectable hybridization signal.

Discussion

We report four cases of anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma (ALK-DLBCL) based on morphologic and immunophenotypic similarity to those previously described.[1–6] ALK-DLBCL was initially described by Delsol *et al* in 1997.[1] Our study of four cases brings the total number of reported cases of ALK-DLBCL in the literature to 33.

ALK-DLBCL has a distinct morphologic appearance with immunoblastic/plasmablastic cytology with round, centrally to eccentrically located nuclei, prominent single central nucleoli, and moderate amounts of variably eosinophilic cytoplasm (Figures 1 and 2). A sinusoidal growth pattern may be seen (Figure 1a). Immunohistochemically, ALK-DLBCL shows features suggesting plasmacytic differentiation, with positivity for EMA, CD138, VS38c, and monotypic cytoplasmic light chain. The characteristic ALK staining is usually cytoplasmic and coarsely granular (attributed to the presence of the *Clathrin-ALK* fusion). Occasional cases with nuclear and cytoplasmic positivity have also been reported (Table 4). CD4, CD57, and CD45 are variably positive, and CD30, EBV, CD43, B-cell related antigens (CD20 and CD79a), and T-cell related antigens (CD3) are negative. Table 5 presents a summary of the frequency of common immunohistochemical findings. Delsol *et al* also found that a majority (5/7) of their cases expressed monotypic IgA lambda, which has also been subsequently reported by others. We and others have found that no cases express CD56 or TIA-1.[4–6]

Although a fairly typical immunohistochemical (plasmacytic) profile has been established for ALK-DLBCL, it is clear that some immunophenotypic heterogeneity exists. In one of our four cases, CD20 highlighted rare positive tumor cells, providing a helpful clue to the underlying B lineage. CD20 positivity, even focal, is distinctly unusual. We show one case with scattered cytokeratin (AE1/AE3)-positive tumor cells, which in conjunction with EMA positivity may lead to an erroneous interpretation of carcinoma. In addition, although usually negative, De Paepe *et al*[3] report one of their three cases as being CD30 positive.

The overall morphologic and immunohistochemical features should allow for distinction of ALK-DLBCL from other entities including ALCL, plasmablastic lymphoma, plasmablastic myeloma,

Table 5 Frequency of immunohistochemical markers in ALK-DLBCL from the literature

Antibody	*Number of positive cases/total numbers of cases tested*	*%*
CD138/VS38	32/32	100
Kappa or lambda Ig	28/31	90
ALK	33/33	100
EMA	31/31	100
CD30	2/32	6
CD45	15/21	71
CD57	8/20	40
CD4	14/22	64
CD20	1/32	3
CD79a	5/31	16

Table 4 Comparison of selected clinical and molecular features from the 33 reported cases of ALK-DLBCL

Author, year (reference)	*No. of cases*	*Age*		*Molecular*	
		Ped.	*Adult*	*ALK rearrangement*	*Technique*
Delsol, 1997[1]	7	1	6	ND (3)	RT-PCR for *NPM-ALK*
Gascoyne, 2003[2]	6[a]		6[a]	*CLTC-ALK*	FISH
De Paepe, 2003[3]	3	2	1	*CLTC-ALK*	FISH
Chikatsu, 2003[4]	1		1	*CLTC-ALK*	RT-PCR
Onciu, 2003[5]	2	2		*NPM-ALK*	RT-PCR
Adam, 2003[6]	1		1	*NPM-ALK*	RT-PCR
McManus, 2004[7]	1		1	*CLTC-ALK*	RT-PCR
Colomo, 2004[8]	1		1	NR	
Ishii, 2005[9]	1		1	NR[b]	
Rudzski, 2005[10]	2		2	Detected[c]	FISH
Gesk, 2005[11]	3	3		*CLTC-ALK*	FISH
Isimbaldi, 2006[12]	1	1		*CLTC-ALK*	RT-PCR
Bubala, 2006[13]	1	1		*CLTC-ALK*	FISH
This study	4		4	Detected (1/1)	FISH

[a]One of the six cases was initially reported by Delsol *et al*.[1]

[b]Only abstract available on Pubmed.

[c]One case reported as consistent with *NPM-ALK*, abstract only available on Pubmed.

Ped, pediatric; FISH, fluorescence *in situ* hybridization; RT-PCR, reverse transcriptase-polymerase chain reaction; ND, none detected; NR, not reported; NA, not applicable.

Table 6 Comparison of selected clinical features of the 33 reported cases of ALK-DLBCL

Author (reference)	*Case no.*	*Sex/age*	*Sites of disease*	*Stage*	*Therapy*	*Present clinical status*
Delsol[1]	1	53/M	Systemic LA, splenomegaly	IVA	CTX plus intrathecal MTX, relapsed, BMT	Dead of disease after 26 months
	2	15/M	NR	I	COPAD-Ara-C	Alive without disease after 156 months
	3	37/M	Mediastinal LA (2)	II (1)	M-BACOD (2)	Cases 3, 4 , 7—dead of disease after 9–33 months
	4	44/M		III–IV (4)	B-CHOP (1)	
	5	67/F			MOPP + XRT (1)	Lost to follow-up after 11 months
	6	51/M			ACVBP (2)	Alive without disease after 14 months
	7	60/M				See case 3
Gascoyne[2]	1	46/M	Supraclavicular and abdominal LA	III	CTX, relapse at 5 months, CTX and XRT	Alive without disease after 27 months
	2	45/F	Inguinal tumor	NA	NA	NA
	3	49/M	Systemic LA, epidural mass	IV	CHOP and XRT, partial response	Alive with progressive disease after 9 months
	4	48/M	Axillary LA	IA	CTX	Alive without disease after 27 months
	5	(Delsol case 1)				
	6	58/M	Supraclavicular LA and subarachnoid involvement	IV	CHOP+Rituximab	Dead of disease after 6 months
De Paepe[3]	1	10/M	Cervical mass	II	ALCL-99 HR followed by SFOP-LMB 96 two years later	Alive without disease after 6 months
	2	13/F	Cervical LA, HSM, mediastinal mass (at relapse)	III	NHL-BFM ALCL99 with ALCL relapse, BMT	Dead of disease after 3 months
	3	26/M	Cervical LA, base of tongue tumor	II	CHOP $\times 4$/VIM $\times 1$/DHAP $\times 1$, neck and upper mediastinum XRT, progressive disease, development of skeletal lesions, hyper-C-VAD, and BMT after BEAM	Alive without disease after 44 months
Chikatsu[4]	1	36/F	Multiple intramuscular tumors, bilateral ovarian tumors, HSM	IV	Combination CTX	Dead of disease after 11 months
Onciu[5]	1	16/M	Scalp and parietal bone mass, cervical, axillary, and inguinal LA, multiple lytic skeletal lesions	IV	LMB 89, poor response, weekly vinblastine, intrathecal CTX, and palliative XRT	Dead of disease after 24 months
	2	10/M	Laryngeal supraglottic mass, cervical and submandibular LA	II	POG8719, XRT to sites of persistent disease and DAHP $\times 3$	Alive without disease after 156 months
Adam[6]	1	35/M	Right cervical and supraclavicular LA	IIA	CHOEP-21 $\times 5$, disease progression, auto BMT, relapse, relapse CTX (adriamycin, bleomycin, vinblastine, decarbazine)	Dead of disease after 14 months
McManus[7]	1	21/M	Pyloric mass	IIE	CHOP $\times 6$	Alive without disease after 2 years
Colomo[8]	1	34/M	Generalized LA	NR	Specifics NR	Dead of disease after 8 months

Table 6 Continued

Author (reference)	*Case no.*	*Sex/age*	*Sites of disease*	*Stage*	*Therapy*	*Present clinical status*
Ishii[9] (abstract only)	1	33/M	Right neck LA, at relapse multiple paraaortic LA, and splenomegaly	NR	CR with chemotherapy and local XRT, relapse at 1 year, CR with CHOP biweekly, relapse allo-PBSCT	Dead of disease after 31 months
Rudzski[10] (abstract only)	1	48/M	Large upper neck mass	IIIB	CHOP $\times 3$	Dead of disease after 3 months
	2	49/M	Abdominal LA, stomach infiltrate	IVB	On chemotherapy	Currently alive
Gesk[11]	1	13/M	Cervical LA	II	ALCL99 SR: multiagent CTX	Partial remission
	2	12/F	Mediastinal mass, cervical LA	II	Multiagent chemotherapy	Alive without disease at 4 years
	3	16/M	Mediastinal mass, cervical LN, chest wall and left pleura involved	IV	Multiagent chemotherapy, BMT	Dead of disease after 1 year
Isimbaldi[12]	1	9/F	Left cervical mass	I	AIEOP LNH 97, CR, ICE at relapse followed by PVDA	Dead of disease after 9 months
Bubala[13]	1	9/M	Ollier disease, generalized LA, mediastinal mass, bony lesions	III	Initial induction with lymphoblastic lymphoma protocol, then LMB 89 protocol, intensification due to disease progression	Dead of disease after 5 months
This study	Four patients, please refer to Table 2					

LA, lymphadenopathy; CTX, chemotherapy; MTX, methotrexate; BMT, bone marrow transplant; NA, not available; NR, not reported; XRT, radiation therapy; HSM, hepatosplenomegaly; DAHP, dexamethosone, cytarabine, cisplatinum; CHOEP-21, cyclophosphamide, adriamycin, vincristine, etoposide, prednisone; CR, complete remission; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; PBSCT; peripheral blood stem cell transplant; ICE, ifosphamide, carboplatin, etoposide; PVDA, prednisone, vincristine, doxorubicin, asparaginase.

anaplastic variant of diffuse large B-cell lymphoma, and carcinoma. ALCL is typically CD30(+), of T-cell phenotype and would be negative for plasma cell markers (CD138) and immunoglobulin light chain. Plasmablastic lymphomas often occur in the oral region of human immunodeficiency virus-infected individuals, and are EBER positive and ALK negative.[15] The anaplastic variant of DLBCL is usually strong CD20(+) and ALK(−). Plasmablastic myeloma has not been reported to be ALK positive, and would be associated with other features such as lytic bone lesions and a monoclonal protein in serum and/or urine.

The clinical features from the 33 reported cases of ALK-DLBCL are summarized in Tables 2 and 6. ALK-DLBCL spans all age groups with an overall male predominance (M:F ratio of 3:1). The M:F ratio is similar in children (7:3) and adults (18:5). Commonly reported clinical features included lymphadenopathy (27 cases), hepato- and/or splenomegaly (four cases), bony/CNS extension (four cases), mediastinal mass (four cases), and laryngeal/oral mass (three cases). Although only 33 cases of ALK-DLBCL have been reported thus far, higher stage disease at presentation (III–IV) appears to correlate with a poor response to multiagent lymphoma chemotherapy and an aggressive clinical course (Table 6). The overall median survival of high stage III/IV patients ($N=13$) was 11 months. Of the 11 patients reported as low stage I/II with at least 14 months follow-up, the average disease-free survival was 41 months ($N=10$). Only one was dead of disease after 14 months (Table 6).

The recent discovery of underlying *ALK* rearrangements in ALK-DLBCL is an important advance in our understanding of the pathogenesis of this lymphoma.[2–6] The *ALK* gene located on chromosome 2p23 may be translocated to either the Clathrin (*CLTC*) gene locus on chromosome 17q23 or to the nucleophosmin (*NPM*) gene on chromosome 5q35, resulting in *CLTC-ALK* and *NPM-ALK* fusion products, respectively[2–6,8–11] (Table 4). Both of these genetic rearrangements were originally identified in classic ALK(+) ALCL, with *NPM-ALK* being distinctly more common (70–80% of cases).[16] As in ALCL, the ALK staining pattern in ALK-DLBCL appears to correlate with the type of underlying rearrangement. Cases with *CLTC-ALK*/t(2;17) rearrangement show a distinctly cytoplasmic and granular *ALK* staining pattern, whereas those cases with an *NPM-ALK*/t(2;5) rearrangement show both cytoplasmic and nuclear staining.[2–6,8–11,16] However, this correlation may be imperfect, as Onciu *et al*[5] reported one case of ALK-DLBCL with *NPM-ALK* fusion that showed cytoplasmic *ALK* staining only. Thus, *ALK* gene rearrangements, originally thought to be uniquely associated with T-/null cell ALCL, have now been convincingly shown to occur in rare cases of B-cell lymphoma.[2–13] Of note, prior to the initial series by Delsol *et al*,[1] Arber *et al*[17] in 1996 reported NPM/ALK fusion transcripts (by RT-PCR) in four of 33 cases of large B-cell lymphoma. Interestingly, and in contrast to the cases of ALK-DLBCL reported thus far, these four cases had a conventional B-cell immunophenotype (CD20+ and CD79a+). All cases were EMA(−) and one case had focal (<10%) CD30 positivity. *ALK* aberrations, specifically involving rearrangements of the *CLTC* gene, have also been identified in some cases of inflammatory myofibroblastic tumors (IMT).[18] Thus, *ALK* overexpression likely contributes to the pathogenesis of a variety of otherwise unrelated neoplasms, ALK-DLBCL, ALCL, and IMT.

Acknowledgements

We thank Rodney Miller, MD, for kindly performing immunohistochemistry for VS38, CD38, and IgA; Randy Gascoyne, MD, for performing FISH analysis for the *Clathrin/ALK* rearrangement on case 3; and Rob McCauley, MD, for contributing case 4.

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