Anaplastic lymphoma kinase-positive large B-cell lymphoma: Clinico-pathological study of 17 cases with review of literature

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Abstract

We retrospectively analysed 17 cases of anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+, LBCL) according to the morphological, immunohistochemical, molecular and clinical features, using which we intend to elucidate the clinicopathological characteristics of this rare entity. In this study, all cases de facto share common features that defined them as a single entity, and various characteristics may expand the spectrum. Among 15 cases, 60% followed an aggressive clinical course with advanced stage and high IPI scores; the median survival of these patients was only 8 months. An analysis showed that both the IPI score and the Ann Arbor stage were significant prognostic factors. Most patients received a chemotherapy regimen including CHOP, CHOEP, EPOCH, and CVAD, and some also underwent localized radiotherapy. However, ALK+, LBCL cases display a dismal clinical outcome and can only be cured with conventional chemotherapy protocols at the stage of localized disease. Novel front-line intensive chemotherapy regimens should therefore be evaluated in this group of patients.

Introduction

Anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+, LBCL) was originally recognized in 1997 by Delsol and colleagues [1] and was listed as a distinct entity in the updated WHO Classification of Haematopoietic and Lymphoid Tissues [2]. It appears to be very rare because it represents less than 1% of all diffuse large B cell lymphomas (DLBCLs), which is partially due to the under-recognition of this disease [2].

Although it is rare, ALK+, LBCL has distinct characteristics and clinicopathological significance. Pathologically, ALK+, LBCL is composed of monomorphic immunoblast-like cells with round pale nuclei that contain large central nucleoli and abundant cytoplasm; ALK+, LBCL also exhibits a sinusoidal growth pattern. Immunohistochemically, the tumour cells co-express ALK (the staining pattern changes according to the gene fusion type and often shows a restricted cytoplasmic staining pattern), a panel of plasma cell markers, CD45, epithelial membrane antigen (EMA) and often contain single light-chain cytoplasmic immunoglobulin A

(IgA). However, tumour cells do not express mature B-cell markers such as CD20. Cytogenetically, chromosomal translocations or rearrangements that involve the ALK locus are regarded as the hallmark of ALK+, LBCL. The most common gene rearrangement is between clathrin (CLTC) and ALK (t (2; 17) (p23; q23)), which results in the CLTC-ALK chimeric protein, although other types of fusions have also been described, such as the SQSTM1-ALK variant translocation [3]. Clinically, ALK+, LBCL is a more aggressive disease than typical DLBCL. In terms of treatment, response to conventional chemotherapy is poor [4]. Due to the limited number of reported cases [5–14], a lack of awareness of this entity, and significant morphologic and immunophenotypic similarities to other haematopoietic and nonhaematopoietic neoplasms, the diagnosis of ALK+, LBCL may be challenging. However, increased awareness of its occurrence and familiarity with its characteristic features are significant for both clinicians and pathologists, particularly with the advancements in emerging therapeutic options [15]. Herein, we present a clinicopathological analysis of 17 cases that delineate the features of ALK+, LBCL at our institution and a review of the literature to foster the idea that this tumour is an individual disease, with the hope that the morphological spectrum will be broadened and that the clinical data will be consummated.

Materials and methods

Patient samples

In all, 17 patients who presented with ALK+, LBCL from 2007 to 2012 were available for study from the surgical pathology and consultation files of the Department of Pathology, Fudan University Shanghai Cancer Center. All cases were histologically and immunohistochemically reviewed by two senior pathologists according to the updated World Health Organization Classification of Tumors of Haematopoietic and Lymphoid Tissues [2] to confirm the diagnosis. Available clinical data including presentations, therapy and follow-up information were evaluated and updated. The stage of disease was determined using the Ann Arbor staging system. Approval for these studies was obtained from the Institutional Review Board.

Histology and immunohistochemistry

All specimens were formalin-fixed, paraffin embedded tissues that underwent routine haematoxylin-eosin (H&E) staining and microscopic observation. The immunohistochemical study was performed on paraffin sections according to the standard EnVision technique using a panel of monoclonal and polyclonal antibodies including those against CD10 (56C6; DAKO; dilution 1:40), Bcl6 (PG-B6P; DAKO; dilution 1:10), MUM1 (MUM1P; DAKO; dilution 1:50), Bcl2 (124; DAKO; dilution 1:50), CD20 (L26; DAKO; 1:50), CD3 (2Gv6; DAKO; dilution 1:80), CD138 (MI15; DAKO; dilution 1:50), ALK (ALK1; DAKO; dilution 1:80), and EMA (E29; DAKO; 1:40), C-MYC (Y69; Epitomics; dilution 1:50). For each antibody, appropriate positive and negative control samples were included. The immunohistochemistry results were reviewed by two independent certified pathologists.

Cytogenetic analysis

Fluorescence in situ hybridization (FISH). FISH analyses were performed on paraffin-embedded tissue sections with probes specific for *ALK* (LSI ALK, Vysis/Abbott, Downer Grove, USA) loci. The probe flanking the *ALK* gene breakpoint at 2p23.3 showed a red signal and a green signal under each corresponding laser. Interpretation of the results was based on the literature [16].

Reverse transcription-polymerase chain reaction (RT-PCR). RT-PCR was performed to amplify the gene rearrangement products of immunoglobulin heavy chain (IGH) and T-cell receptor (TCR). Total RNA was extracted from formalin-fixed, paraffin-embedded sections according to the manufacturer's instructions. Synthesis of the first complementary DNA (cDNA) strand was performed by MMLV reverse transcriptase, which was followed by polymerase chain reaction (PCR) amplification. The PCR primers were designed according to the common *ALK* fusion gene type [S1 Table]. DNA sequencing was also used to confirm the *ALK* fusion gene type.

Statistical analysis

Survival was determined from the time of diagnosis until the time of death or last follow-up. Survival curves were constructed according to the Kaplan-Meier method. Survival distributions were compared with the log-rank test. All statistical analyses were performed using STATA, version 11.0 (Stata Corporation, College Station, TX). The column graph was constructed with Graphpad prism, version 5.0. Fisher's exact test was also performed. All *p*-values were two sided, and a *p*-value ≤ 0.05 was considered statistically significant. Protein expression levels were judged by H-score (positive staining intensity by positive percentage) standard.

Results

Clinical features

Clinical information on the 17 cases was summarized in Table 1. These cases showed a remarkable male predominance with a ratio of 16:1. The average age was 39.6 years old and ranged from 12 to 72 years. Thirteen cases presented as lymphadenopathy, of which 10 cases were located in the cervical region; 5 cases presented as retroperitoneal lymphadenopathy accompanied by abdominal pain and inguinal lymph node enlargement. Extranodal occurrence was observed in 2 cases and involved the duodenum and tonsil. Bone marrow involvement was also observed in 4 cases. Nine (60%) patients presented with B symptoms. The serum lactate dehydrogenase (LDH) level was elevated in 15 documented patients, and HIV serology was negative. All patients but one underwent complete staging with clinical examination and radiologic studies. Among 16 documented patients, the majority experienced an aggressive clinical course; among these, cases of stage III-IV disease accounted for a large proportion (11/16) according to the Ann Arbor criteria. The International Prognostic Index (IPI) score was available for 15 patients. Based on the results of the IPI score, we divided the patients into two groups: the low-risk (score 0–2) group and the high-risk (score 3–5) group. The low-risk group contained 5 patients while the high-risk group contained 10. For the 5 low-risk cases, four were early stage (stage I-II) cases, and only one was in stage III-IV; all cases in the high-risk group were in an advanced stage (stage III, IV, *p* = 0.5509) (Fig 1A).

Treatment and outcome

Among the 16 documented patients, 10 were treated with CHOP or CHOP-like regimens for six cycles, and 5 were treated with an E-POCH/CHOEP regimen. Among them, 5 patients were treated with additional radiotherapy at as dose of 30 Gray. Two patients were treated with hyper-CVAD and multiple chemotherapy regimens after relapse. The duration of follow-up ranged from 1 to 90 months (mean time, 40.5 months). Information on the clinical outcomes was available for 15 patients. Most patients experienced an aggressive clinical course: 6 of them died within the first year, and one even died before treatment. For those who died of disease, the average survival and median survival were 8.6 and 8.0 months, respectively, and

Table 1. Clinical information and follow up data of 17 patients.

Case	Gender/Age (y)	Involvement	Stage	Serum LDH	IPI score	Treatment	Survival (months)
1	M/23	mediastinal, retroperitoneal	IIIA	elevated	4	CHOP/E-POCH	10/DOD
2	M/72	Bilateral submandibular, cervical	IVA	elevated	5	CHOP/E-POCH	NA/NA
3	M/57	bones, bilateral cervical lymph node, mediastinal	IVB	elevated	4	CHOP	3/DOD
4	M/55	Bilateral cervical lymph node	IIA	normal	1	CHOP/E-POCH plus RT	48/Alive
5	M/25	Right cervical lymph node	IIA	411	2	CHOP plus RT	24/Alive
6	M/32	Right cervical lymph node	NA	207	NA	CHOP plus RT	6/DOD
7	M/68	Right cervical lymph node, retroperitoneal	IIIA	elevated	4	CHOP	10/DOD
8	M/33	Left supraclavicular, mediastinal, perigastric	IIIB	346	3	CHOP+MX+VP-16+BLM+DXM plus RT plus HYPER-CVAD-A	24/DOD
9	M/12	Cervical lymph node	IA	NA	NA	CHOP	6/Alive
10	M/22	Cervical lymph node, subraclavicular	IIIB	177	2	CHOP	27/Alive
11	M/26	Duodenum	IE	183	1	NA	NA/NA
12	M/42	Left tonsil, retroperitoneal	IVB	237	4	CEHOP	10/Alive
13	M/54	Left cervical	IIB	200	0	CHOEP plus RT plus HYPER-CVAD-A and HYPER-CVAD-B	8/Alive
14	M/20	Left groin, retroperitoneal, bone marrow	IVB	367	3	CHOP	6/Alive
15	M/52	Systemic lymph nodes	IVB	300	4	CHOP plus RT	6/DOD
16	F/47	Left groin, mediastinal	IVB	242	4	without regimens	1/DOD
17	M/34	Left cervical, bilateral hilar, retroperitoneal	IIIB	194	3	CHEOP	3/Alive

Abbreviations: LDH, lactate dehydrogenase; M, male; F, female; CHOP, cyclophosphosphamide, doxorubicin, vincristine, and prednisone; CHOEP/ E-POCH, cyclophosphosphamide, doxorubicin, vincristine, and prednisone with etoposide or bleomycin; RT, radiotherapy; DOD, dead of disease; NA, not available.

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the 5-year OS was only 40% (Fig 1B). Patients with stages I-II disease had a significantly better 5-year OS (100%) than those with stages III-IV disease (5-y OS, 20%), as illustrated in (Fig 1C, $p = 0.0128$). Moreover, the OS of the low-risk group was also better compared with that of the high-risk group (Fig 1D) ($p = 0.0316$). Complete remission could be achieved in all patients who were categorized with early-stage disease (I-II), but only 55% of the patients with end-stage disease (III-IV) achieved complete remission. Among those who experienced complete remission, 2 patients experienced relapse and eventually succumbed to the disease, even if they were treated with hyper-CVAD and multiple chemotherapies. Seven patients who had died of the disease all belonged to the high-risk group and the stage III-IV group. Younger patients (under 30 y) had a significantly better OS than older patients (over 30 y) ($p = 0.114$) (Fig 1E). The Kaplan-Meier curve showed that the OS of the group that received the E-POCH/CHOEP regimen was better compared with that of the group that received the CHOP regimen ($p = 0.185$) (Fig 1F).

Pathological features and Immunohistochemical findings

Histologically, the tumours showed a diffuse infiltration of neoplastic cells in most cases. Sinu-soidal invasion was observed in 5 cases, and this phenomenon was remarkable in cases that involved the lymph nodes. The neoplastic cells were uniformly medium- to large-sized with
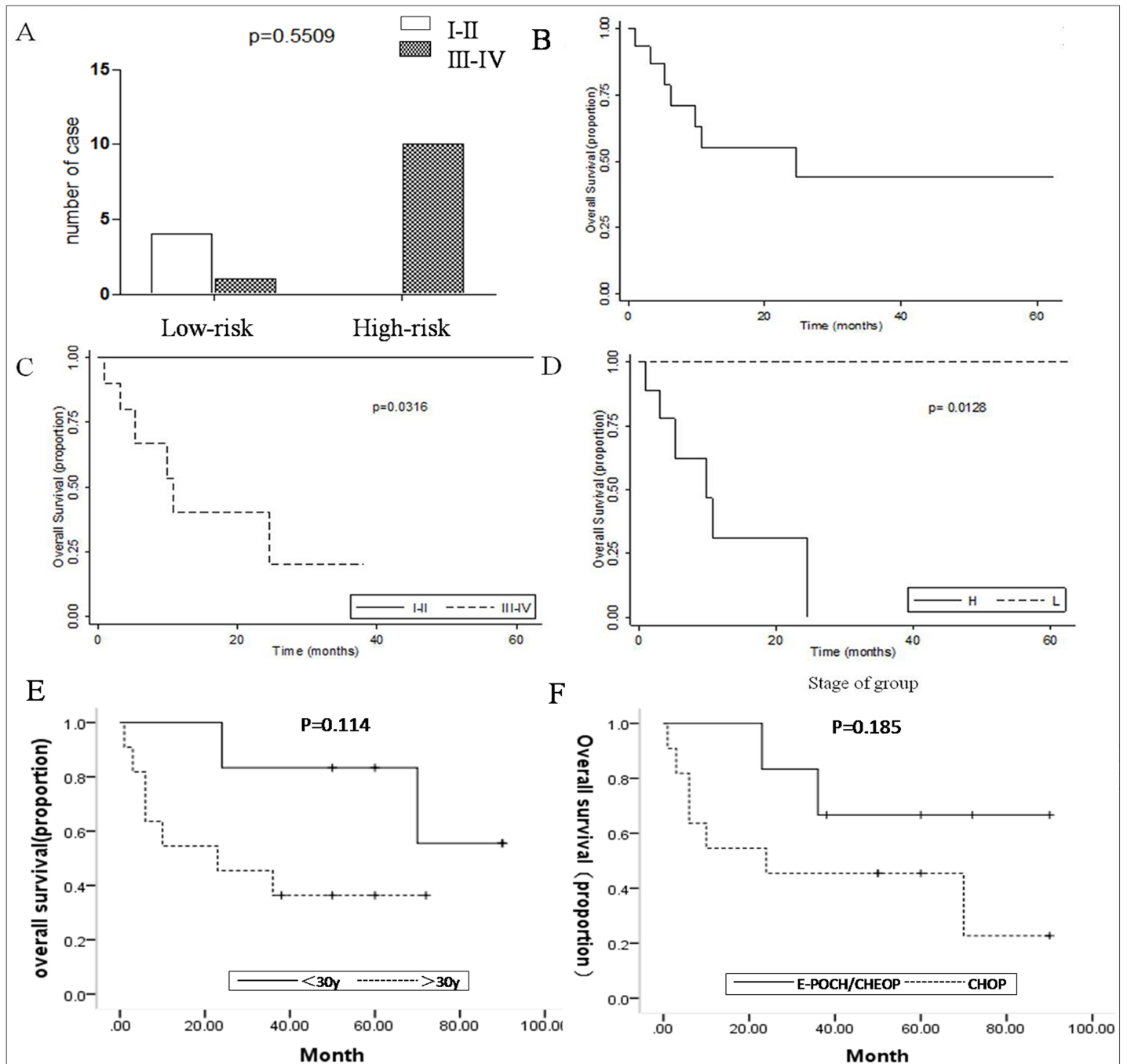
Fig 1. A: Distribution of both low- and high-risk groups according to the Ann Arbor staging criteria B: OS of all the cases C: OS of the low-risk and high-risk groups. D: Ann Arbor staging significantly impacted the OS. E: OS of the <30 y and >30 y groups. F: OS of the CHOP and CHOEP/E-POCH regimen groups.

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round nuclei; they also featured dispersed chromatin and single, central, prominent nucleoli. Typical, moderate amounts of eosinophilic to amphophilic cytoplasm were present, and the tumour cells presented with an extremely obvious plasmablastic/immunoblastic differentiation in almost every case. A large number of multinucleated giant neoplastic cells were obvious in 3 cases. This characteristic may frequently be found in older patients with high IPI scores
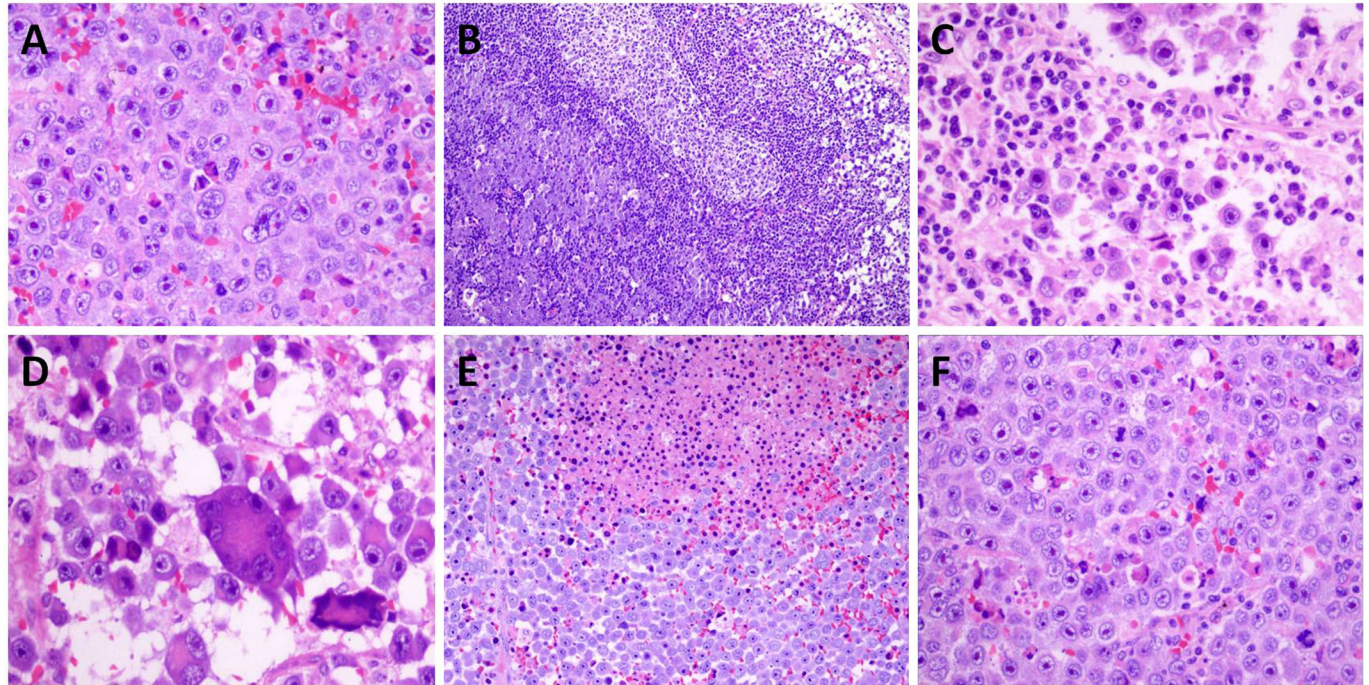
Fig 2. Histopathologic features of ALK-positive diffuse large B cell lymphoma. (haematoxylin & eosin). A: Medium- to large-sized cells with prominent nucleoli B: Sinusoidal Invasion C: plasmablastic/immunoblastic differentiation D: Multinucleated giant neoplastic cells E: Focal necrosis F: frequent mitosis.

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and advanced stage disease. Focal necrosis was also observed in 3 cases. Small lymphocytes and plasma cells were present in varying proportions among the tumour cells (Fig 2). Details of the immunohistochemical findings are summarized in S2 Table. The tumour cells were positive for B-lineage markers including Oct-2 and Bob-1 as well as ALK in all cases, while a large proportion of cases were positive for plasma cell markers including CD38, CD138, MUM1 and VS38C (more than 75%). What's more, C-MYC was also performed in 13 cases, the H-score were significant lower than that in Plasmablastic lymphoma (PBL) or diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) ($p<0.001$) (Fig 3).

Molecular analysis

FISH was performed on 5 cases, and all of them showed a split of the dual-colour probe flanking *ALK*, which indicates a chromosomal break within the *ALK* gene (Fig 4A). Among these, chromosomal breaks were also detected by RT-PCR in four cases (Fig 4B), which suggests that the fusion partner was *CLTC*; this was further confirmed by DNA sequencing (Fig 4C). PCR analysis for *IGH* and *TCR* gene rearrangements was also performed, and 13 cases indicated monoclonal *IGH* rearrangement. No monoclonal *TCR* gene rearrangement was detected.

Discussion

Review of 151 cases

Approximately 134 cases of ALK+ LBCL have been reported in the literature [17–19]. The brief clinicopathologic features of the cases from the literature and those from our institution are all summarized in Table 2. ALK+ LBCL was observed predominantly in male patients, with a male to female ratio of 3.5:1. The average age of the patients was 38.4 years, and it

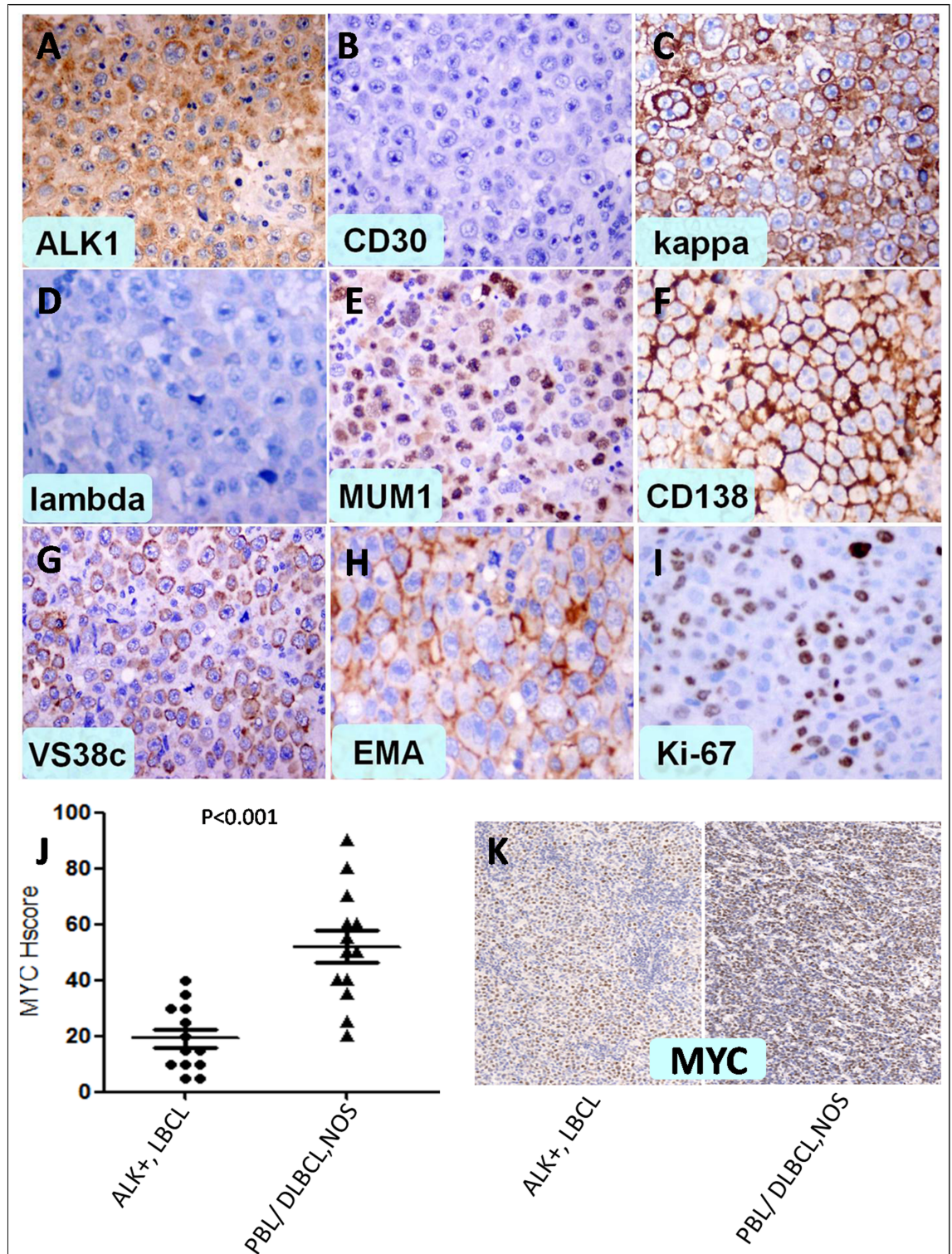**Fig 3.** A: Monomorphic lymphoma cells expressing ALK with a cytoplasmic granular staining pattern B: Negativity for CD30 C, D: Kappa and Lambda show light chain restriction E, F, G, H: Expression of MUM1, CD138, VS38C and EMA I: Ki-67 staining shows a high proliferation index J, K: H-score were significant lower than that in Plasmablastic lymphoma (PBL) or diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS).
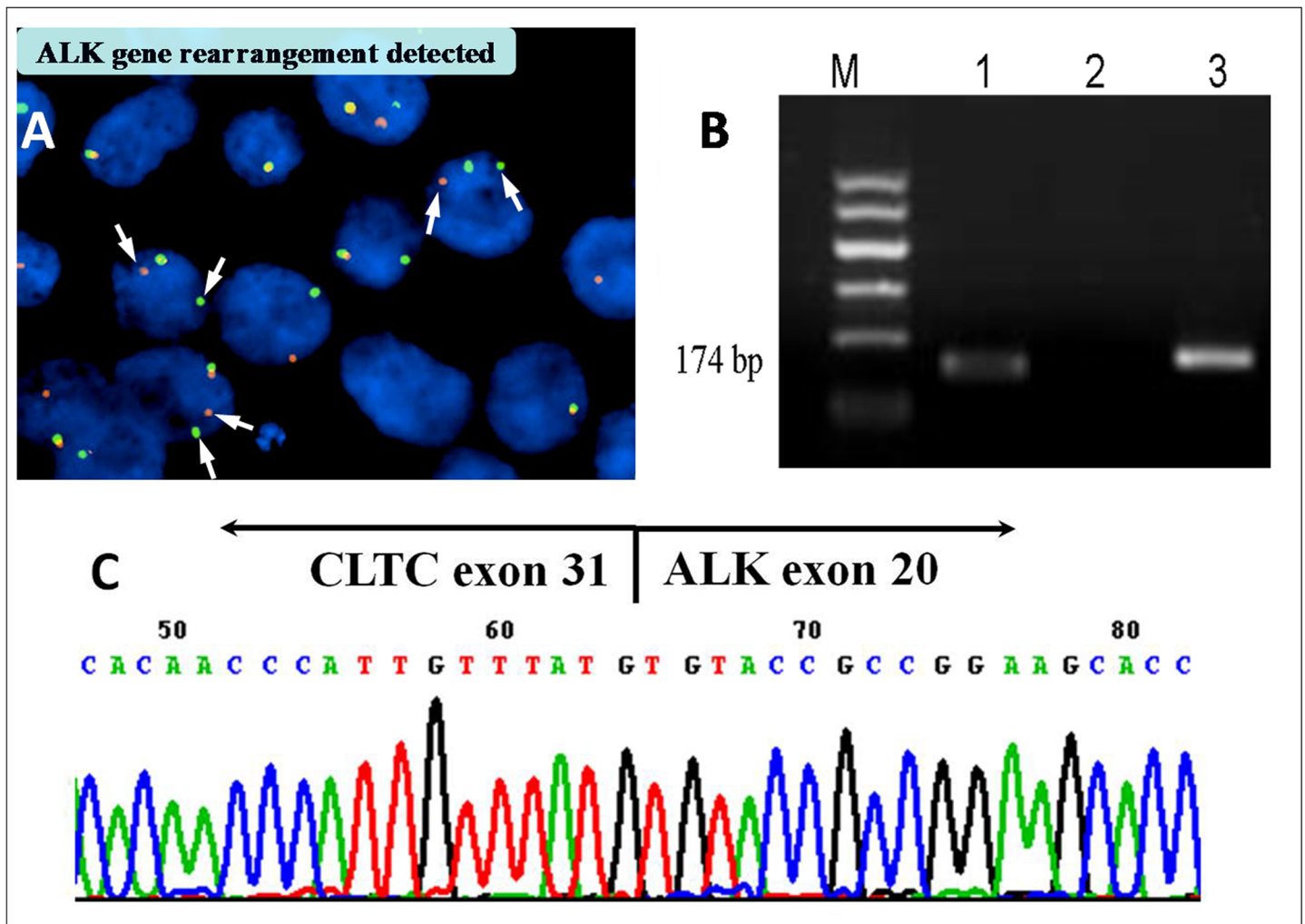
Fig 4. A: Positive FISH for the ALK break apart probe (white arrows). B: PCR electrophoretic band; M: Molecular weight marker, Lane 1: CLTC-ALK, Lane 2: Negative control, Lane 3: PGK. C: DNA sequencing suggests that the fusion partner is CLTC.

ranged from 9 to 72 years. From an analysis of 106 patients whose records contained detailed information on age, only 18.9% (20/106) occurred in a paediatric population (18 y of age or younger). ALL cases in this study and those reported in the literature were positive for ALK protein. By EBER-ISH, EBV was not detected in any of the 87 cases. Detection of *IGH* and/or *IGK* gene rearrangement was performed in 43 cases, 34 (86%) of which showed positive B-cell monoclonality. Conventional cytogenetic and FISH assays detected *ALK* rearrangements in 94.7% (72/76) cases of ALK+ LBCL in our study and in the literature review [20,21]. Thirty-three cases had documented partner genes of *ALK* rearrangements, mostly *ALK-CLTC*, as noted in 75.7% of the cases (28/37); other partner genes included *NPM1* (4 cases), *SEC31A* (3 cases), *SQSTM1* (1 case), *RANBP2* (1 case), and IGL (1 case) [22–29].

Prognostic factors of ALK+ LBCL

ALK-positive LBCL is an aggressive subtype of diffuse large B cell lymphoma as more than 76% of the documented cases were in stage III-IV. In our study, we found that both the IPI score and the stage were significant prognostic factors [Fig 1C and Fig 1D]. The survival of

Table 2. Summary of the clinicopathologic fueatures of the ALK+, LBCL cases of our study and the reviewed literatures.

	Our study	Literature	Total (%)
Male/female	16/1	99/28	115/29
Average age	39.6 (n = 17)	38.4 (n = 129)	39 (n = 146)
Primary sites(nodal/extranodal)	15/2	98/28	113/30
B symptoms	9/15	17/34	26/49 (53)
Bone marrow involvement	2/17	19/63 (30)	11/80 (13)
Clinical stage(I-II vs. III-IV)	4/11	43/58	47/69(68.1)
Average follow-up(mo)	40.5(n = 17)	23.8 (n = 92)	32.1 (n = 109)
Outcome(died/alive)	8/15	45/46	53/61
ALK	17/17	125/125	142/142 (100)
Bob.1	5/5	18/18	23/23 (100)
CD3	0/17	0/71	0/88 (0)
CD4	2/9	35/66	37/75 (49.3)
CD20	2/15	4/120	6/135 (4.4)
CD30	1/15	14/117	15/132 (11.4)
CD79a	3/9	21/108	24/117 (20.5)
CD138	9/11	101/107	110/118 (93.2)
IgA	0/2	60/75	60/77 (77.9)
K	5/9	25/61	30/70 (42.9)
λ	4/9	36/68	40/77 (51.9)
MUM1	8/9	45/54	53/63 (84.1)
Oct-2	7/7	20/23	27/30 (90)
EBER ISH	0/17	0/70	0/84 (0)
ALK rearrangement	4/5	67/71	71/76 (93.4)
IGH PCR	13/17	24/26	37/43 (86)

patients in the high-risk group appeared to be worse than that of patients in the stage III-IV group, and the reason for this may be that a low IPI score case was categorized into the advanced stage group, which is what we can learn from Fig 1A. This case was considered stage III because of the wide range of involved lymph node regions. However, in terms of age, physical condition and other laboratory examination indices, this patient still belonged to the low-risk group. Additionally, younger patients (under 30 y) had a significantly better OS than older patients (over 30 y), but according to the *P*-value, the difference was not statistically significant. It was reported in the literature that patients younger than 35 years had a significantly better OS than those older than 35 years [19].

Conventional therapies for ALK+, DLBCL

Our study was the second large cohort that suggested that ALK-positive LBCL lacks CD20 in all cases. Therefore, the efficacy of Rituximab is insufficient for the improvement of the outcome in this subset of cases. From a clinical perspective, ALK+, LBCL should be distinguished from typical DLBCL, which requires a distinct treatment. According to our review, most patients received chemotherapy, including CHOP, CHOEP, EPOCH, and CVAD, and some of them also underwent localized radiotherapy and haematopoietic stem cell transplantation. However, patients with ALK+ LBCL still displayed a dismal clinical outcome compared with patients with typical DLBCL who were treated with CHOP or CHOP-like regimens. Similarly, approximately 37.5% of cases at our institution received more rigorous chemotherapy such as E-CHOP, CHOEP, or E-POCH/CHOEP; these regimens do help to improve the survival

compared with the CHOP regimen, but according to the *P*-value, the difference among regimens was not statistically significant [Fig 1F]. Additionally, both the analysis of our cases and a review of previously reported cases show that ALK + DLBCL can be an aggressive malignancy that can be cured with conventional chemotherapy protocols only at the stage of localized disease [19].

Novel front-line therapy regimens

The highly aggressive nature of this lymphoma and the relative paucity of molecular data available highlight the need for deeper insights into the molecular pathogenesis of ALK-positive large B-cell lymphomas to identify new and effective alternative treatments. One research indicated that ALK-positive large B-cell lymphomas express a complete plasmablastic differentiation program but, contrary to plasmablastic lymphomas, do not have MYC rearrangements [30]. It was consistent with the low MYC expression level in our study, which suggested that MYC may not be the main molecular pathogenesis for the highly aggressive nature of ALK+, LBCL. Recent developments have led to significant diagnostic and therapeutic advances, including efficient diagnostic tests and ALK-targeting agents that are readily available in the clinical setting. Inhibition of ALK activity resulted in sustained tumour regression in a xenotransplant tumour model. These data indicate a role for CLTC-ALK in the maintenance of the malignant phenotype, which provides a rationale for a therapeutic target for these otherwise refractory tumours [31, 32]. To further study their therapeutic potential in ALK+, LBCL, a CTLC-ALK-positive LBCL cell line (LM1) was established as a preclinical model to study the role of CLTC-ALK activity in DLBCL lymphomagenesis. It was demonstrated that these lymphomas display activation of ALK signalling pathways and are potently suppressed in vitro and in vivo by a selective ALK inhibitor. The selective ALK inhibitor NVP-TAE684 repressed ALK-activated signalling pathways and induced apoptosis of LM1 DLBCL cells [33, 34]. Based on the molecular pathology described above, the recent introduction of the small molecule ALK inhibitor crizotinib may provide a potential new therapeutic option for patients with this disease.

Unquestionably, research on different therapies has been very productive in recent years and will most likely continue to be in the future. Another recent study suggests that ALK expression in DLBCL is strictly linked to STAT3 phosphorylation. STAT3 would be one of the molecular targets in ALK-positive DLBCL. The relevance of the ALK/STAT3 pathway in the pathogenesis of ALK-positive large B-cell lymphomas indicates that this pathway is an attractive target for new therapies [35, 36]. Specifically, STAT3 inhibition also serves as a possible therapeutic target for lymphomas with the SQSTM1-ALK variant translocation [37].

Conclusions

ALK-positive large B cell lymphoma is a rare tumour with characteristic pathological and clinical feature. Morphologic analysis, immunohistochemistry and genetic tests show that the *ALK* gene is associated as an external cause of the disease but that the disease is part of a spectrum. ALK +, LBCL is defined as a separate entity but may belong to this broad spectrum. The recognition of ALK+, LBCL as a distinct entity is important because most patients experience an aggressive disease course and are candidates for novel treatment approaches. Further prospective studies are needed to optimize therapies for this disease.

Supporting information

S1 Table. Primers for the detection of ALK fusion transcripts.
(DOCX)

S2 Table. Summary of immunohistochemical findings.
(DOCX)

S1 Data. URLS and DOIs of S1 Table and S2 Table.
(DOC)

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Investigation: XNJ.

Methodology: XQL WGW.

Project administration: XYZ.

Resources: XQL.

Software: XNJ.

Writing – original draft: XNJ BHY.

Writing – review & editing: XNJ.

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