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Original Article

Promising response of anaplastic lymphoma kinase-positive large B-cell lymphoma to crizotinib salvage treatment: case report and review of literature

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Abstract: Anaplastic lymphoma kinase (ALK)-positive diffuse large B-cell lymphoma (ALK + DLBCL) is a rare and poorly characterized subtype of lymphoma. Reports suggest that this type of tumor responds poorly to standard regimens for non-Hodgkin's lymphoma, with rituximab playing no therapeutic role due to the absence of CD20 expression. In view of the expression of ALK in this disease, it is plausible that the ALK inhibitor crizotinib may be an effective treatment. We report a case of a 21-year-old male ALK + DLBCL patient. He initially received five cycles of CHOP-21 (vincristine, pirarubicin, cyclophosphamide and prednisone) and achieved a partial remission (PR) but soon deteriorated. He was subsequently treated with five courses of the salvage chemotherapy regimen ICE (ifosfamide, carboplatin and etoposide) and achieved PR again. He refused to accept an autologous stem-cell transplantation, after which the disease progressed rapidly. We administered two courses of an alternative salvage chemotherapy regimen containing GEMOX and dexamethasone with the addition of the ALK inhibitor crizotinib. His symptoms alleviated for a short time but soon worsened and the patient died of massive progressive disease.

Keywords: Anaplastic lymphoma kinase, non-hodgkin lymphoma, spleen, crizotinib

Introduction

Anaplastic lymphoma kinase- (ALK-) positive diffuse large B-cell lymphoma (ALK + DLBCL) is a rare neoplasm recognized as a separate entity by the latest WHO classification of hematological malignancies [1]. It usually affects young adults and has a male predominance. The chromosomal translocation t (2; 17) (p23; q23) is the most commonly reported cytogenetic abnormality in this disease, which leads to fusion of the genes *CLTC* (clathrin) and *ALK* [5]. Most patients present at an advanced stage, follow an aggressive clinical course and have poor outcome. Although characteristically a nodal disease, extranodal involvement has been reported [2-4]. We present a case in which the patient presented with extranodal involvement of the spleen in keeping with previously reported cases [3, 8]. Histologically, the tumor cells had a plasmablastic or immunoblastic appearance, with a sinusoidal pattern of infiltration, and a unique immunophenotypic profile largely characterized by lack of expression of CD20, and positivity for plasma cell markers such as CD138, epithelial membrane antigen (EMA), and multiple myeloma oncogene 1 (MUM1).

In reporting this case we would like to highlight the aggressive nature and high recurrence rate of this subset of DLBCL as well as its poor response to conventional chemotherapy. The recent introduction of the small molecule ALK inhibitor crizotinib provides a potential new therapeutic option for patients with this disease that warrants further investigation.

Case report

In December 2012, a 21-year-old male was admitted with abdominal pain of the left quadrant for 3 days. He had no fever, night sweats or weight loss and reported no history of other diseases. Abdominal computed tomography (CT) revealed splenomegaly with retroperitoneal

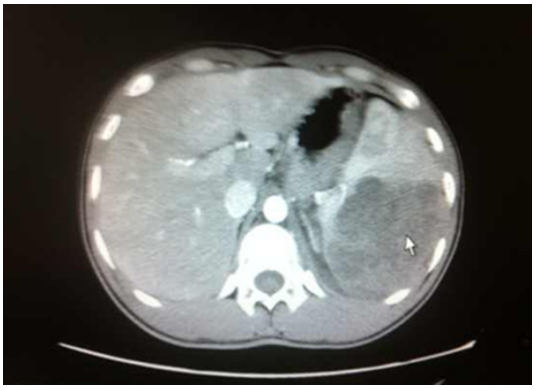

Figure 1. Mass in the spleen by CT scan (shown by the arrow).

lymphadenopathy and a low-density mass in the body and tail of the pancreas (**Figure 1**). Splenectomy was performed on January 15th 2013, histopathological analysis revealed a diffuse infiltration of tumor cells that were rich in plasma with vesicular chromatin and prominent nucleoli. The tumor cells lacked of expression EMA and CD20, but were highly positive for CD138, MUM1, CD4 and cytoplasmic ALK, whereas only single cells showed expression of CD30 and CD38 (**Figure 2**). Additional immunohistochemistry results are provided in **Table 1**. Clonal rearrangements of IGH-FR1 and IGκ-VJ were detected by PCR (**Figure 3**), and EBER (Epstein-Barr virus) immunohistochemical staining was negative. An *ALK* gene rearrangement was detected by FISH (**Figure 4**), while RT-PCR detected a *CLTC-ALK* fusion transcript which was confirmed by Sanger sequencing (**Figure 5**). Relevant clinical and cytogenetic data of the patient is summarized in **Table 1**. Positron emission tomography–computed tomography (PET-CT) revealed enlarged hypermetabolic lymph nodes in the patient's left neck, left adrenal area, hepatic portal, lesser omentum and retroperitoneal space with some of them fused. Thus the patient was diagnosed with "splenic ALK + DLBCL, Stage III, Group A" with an IPI score of 3. The patient was assigned into the moderate-high risk group and prescribed five cycles of CHOP-21 (vincristine 1.4 mg/m^2 iv d1; pirarubicin 60 mg/m^2 iv d1; cyclophosphamide 750 mg/m^2 iv d1; and prednisone 50 mg po bid d1-5) were administered with abdominal pain relieved after one cycle of the regimen. Reassessment by PET-CT in May 2013 showed that multiple lymph nodes in the patient's abdomen had shrunk with average standardized uptake (SUV) values returning to normal while retroperitoneal lymph nodes had increased both in number and 18F-FDG metabolism rate with a maximum SUV value of 10.2. We subsequently changed the protocol from CHOP to ICE (etoposide 0.1 g/m^2 iv d1-3; carboplatin 600mg iv d2; and IFO 5 g/m^2 iv d2), but after one course the patient discontinued treatment. In October 2013 the patient was admitted in hospital again with mild fever and lumbodorsal pain. Multiple lymph nodes in the left neck and abdomen were enlarged with markedly increased SUV values. After another four cycles of ICE with an interval of 21 days, PET-CT performed on March 15th 2014 revealed decreased SUV values and shrinking of lymph nodes in the neck and abdomen but irregular soft tissue shadows were observed in the anterior mediastinum and pelvic cavity. With symptoms relieved, the patient refused to accept therapy up to October 7th 2014, by which time the disease was rapidly progressing. He presented with left cervical lymphadenopathy and persistent backache. Lactate dehydrogenase (LDH) levels were exorbitantly increased (858u/l). After two courses of GEMOX plus Dexamethasone with the addition of ALK inhibitor crizotinib (Gemcitabine 1 g/m^2 iv d1; 8 Oxaliplatin 100 mg/m^2 iv d1; Dexamethasone 10 mg/m^2 iv d1-8; and Crizotinib 250mg po bid), his symptoms were relieved with CT revealing decreased lymphadenopathy. The LDH level also fell to 568 u/l for a short time. Unfortunately the disease progressed rapidly with increased LDH and platelets (**Figure 6**). Abdominal CT showed a polyserositis and the patient died two months later.

Discussion

ALK + DLBCL was first reported by Delsol et al in 1997 based on a series of seven cases and was officially defined as a new subtype of lymphoma by the WHO in 2008 [6]. To date, less than 100 cases have been reported. The disease spans all age groups (9 to 72 years), with a median of 38 years and occurs with a male: female ratio of 3:1 [5]. It most frequently presents with painless enlarged lymph nodes, predominantly located in the neck and mediastinum, and extra nodal involvement of nasopharynx, tongue, bone, gastrointestinal tract, liver, spleen and ovary [2-4]. Involvement of the spleen, as observed in the present case, is

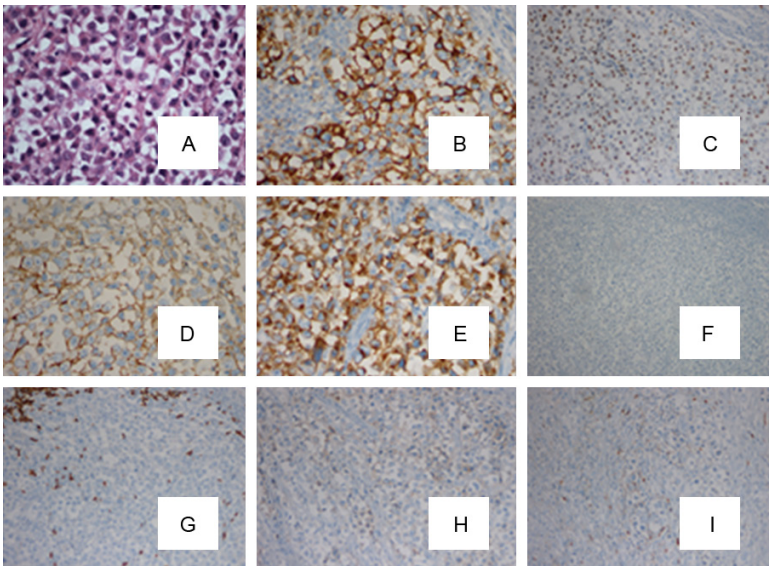

Figure 2. HE×400 times (A) and IHC staining of the spleen mass. The tumor tissue strongly expressed CD138 (B), MUM1 (C), CD4 (D) and Cytoplasmic granular staining of ALK (E), but negative for EMA (F) and CD20 (G). Weak expression of CD30 (H) and CD38 (I) was observed.

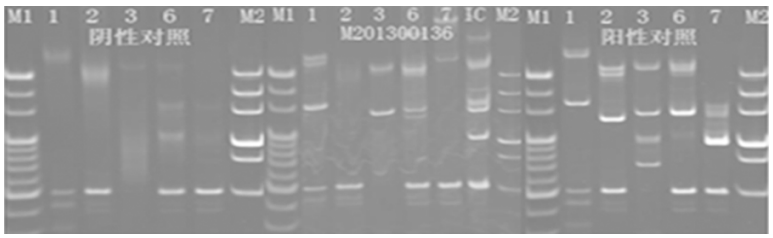

Figure 3. Clonal rearrangements of IGH-FR1, IG K-VJ were detected by PCR. M1 and M2 representative markers, IC within the control sample, showing tube one and six amplified in line with the target size of the amplified bands.

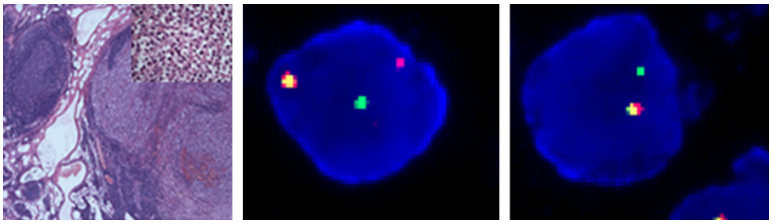

Figure 4. HE staining of spleen tumor tissue (40×; left panel) and Fluorescence in-situ hybridization (FISH) revealed a genomic break in the ALK1 locus (middle panel) while in some tumor cells there was also evidence of partial loss of the rearranged ALK gene (right panel).

rarely seen. In contrast, the morphological features and IHC staining of the neoplastic cells was similar to those of previously reported cases (see **Table 1**), being intermediate to large sized and immunoblastic or plasmablastic in appearance with a single prominent central nucleus and moderate amounts of eosinophilic to amphophilic cytoplasm. Cells were generally positive for CD138, ALK, MUM1 and IgA, weakly positive for CD30 and CD38, and negative for CD20. We identified an *ALK* rearrangement by FISH and detected the *CLTC-ALK* transcript by RT-PCR, thus further confirming the diagnosis.

Interestingly, EMA was found to be negative in our patient. To our knowledge this is only the second reported case of EMA-negative ALK + DLBCL. EMA is aberrantly glycosylated and overexpressed in a variety of epithelial cancers, and plays a crucial role in progression of the disease. Tumor-associated EMA differs from the EMA expressed in normal cells with regard to its biochemical features, cellular distribution, and function. In cancer cells, EMA participates in intracellular signal transduction pathways and regulates the expression of its target genes at both the transcriptional and post-transcriptional level, and thus may provide a possible therapeutic target [7].

The *ALK* gene encodes a tyrosine kinase receptor belonging to the insulin receptor superfamily, which is normally silent in lymphoid cells [9]. Indeed, ALK protein is rarely expressed in normal tissues and its expression in malignancy is often companied by causal chromosomal aberrations. ALK protein localization is determined by the specific chromosomal translocation, of which t (2; 17) (p23; q23) is most commonly seen, resulting in a *CLTC-ALK* fusion gene and ALK protein local-

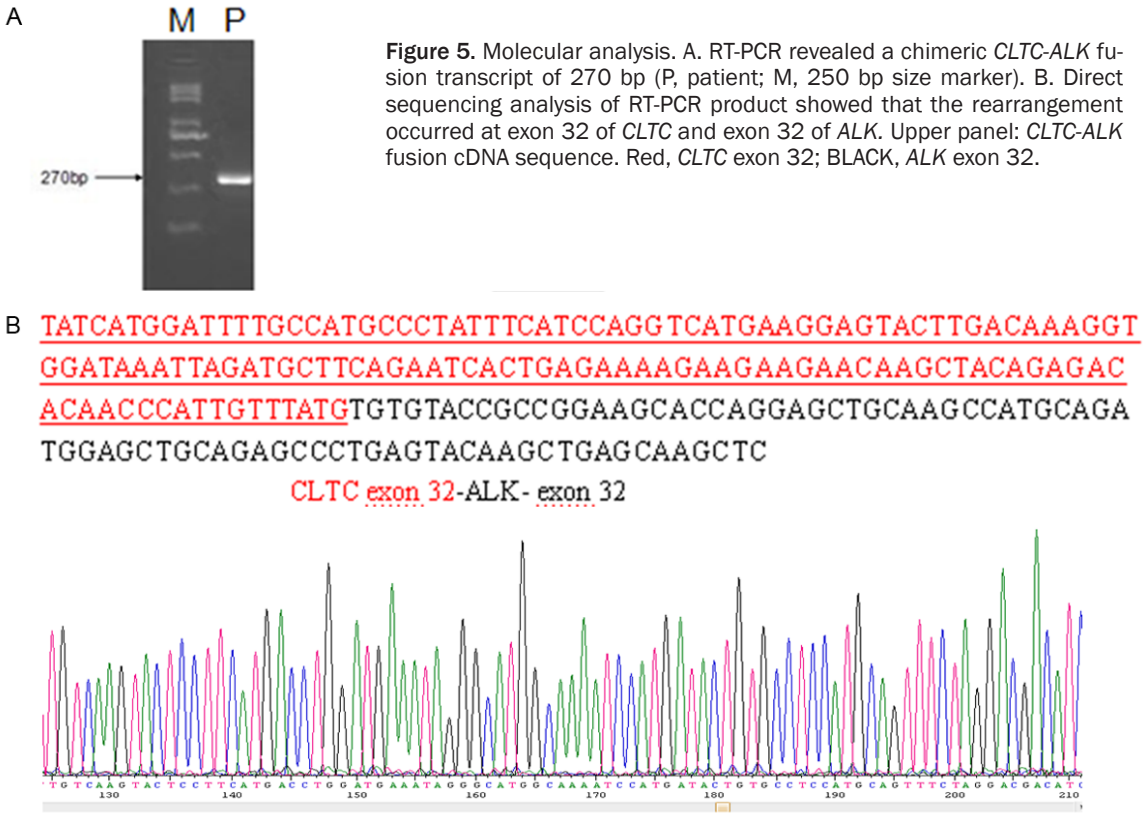

Figure 5. Molecular analysis. A. RT-PCR revealed a chimeric *CLTC-ALK* fusion transcript of 270 bp (P, patient; M, 250 bp size marker). B. Direct sequencing analysis of RT-PCR product showed that the rearrangement occurred at exon 32 of *CLTC* and exon 32 of *ALK*. Upper panel: *CLTC-ALK* fusion cDNA sequence. Red, *CLTC* exon 32; BLACK, *ALK* exon 32.

Table 1. Relevant clinical and cytogenetic data of the patient

Case	Sex/ age	Stage	Treatment	Response/- survival	ALK staining	Morphology	Immuno- phenotype	PCR analysis	Karyotype	FISH - identification	RT- PCR	EBV
1	M/24	IIIA	CHOP-21×5	Dead after 24 months of diagnosis	Cyto- plasmic granular	Large cell with plasmatic dif- ferentiation	CD138+	IGH-FR1	46, XY [11]	ALK rearrange- ment	CLTC- ALK	Negative
			ICE×5				CD4+	IGK-VJ				
			Gemox+Dex+- crizotinib×2				MUM1+					
							ALK+					
							λ+					
							CD30+weak					
							CD38+weak					
							CD43+weak					
							CD57+weak					
							CD20-					
							CD15-					
							CD79a-					
							CD3-					
							CD7-					
							S100-					
							LCA-					
							K-					
							CK-					
							EBER-					

ized to the cytoplasm. A nucleophosmin (*NPM*)-*ALK* fusion gene formed by t (2;5) (p23;q35) translocation is also recurrent in this disease, and is associated with ALK protein localized to

Table 2. Summary of treatment and outcome of previously reported ALK + DLBCL cases

Author	Case no.	Sex	Age	Stage	First therapy	Slvage therapy	Present clinical status
Delsol1 [1]	1	M	53	IVA	CTX plus intrathecal MTX	BMT	Died of disease after 26 months
	2	M	15	I	COPAD+Ara-C		Alive without disease after 156 months
	3	M	37	II	M-BACOD×2		Case 3, 4, 7 died of disease after 9~33 months
	4	M	44	III~IV	B-CHOP		See case 3
	5	F	67		MOPP+XRT×1		Lost to follow up after 11 months
	6	M	51		ACVBP×2		Alive without disease after 14 months
	7	M	60				See case 3
Gascoyne [2]	1	M	46	III	CTX	CTX+XRT	Alive without disease after 27 months
	2	F	45	NA	NA		N/A
	3	M	49	IV	CHOP+XRT	PR	Alive with progressive disease after 9 months
	4	M	48	IA	CTX		Alive without disease after 27 months
	5 (Delsol case 1)	M	53				
	6	M	58	IV	CHOP+Rtiuximab		Died of disease after 6 months
De Paepe [3]	1	M	10	II	ALCL-99	SFOP-LMB96	Alive without disease after 6 months
	2	F	13	III	NHL-BFM ALCL99	BMT	Died of disease after 3 months
	3	M	26	II	CHOP×4VIM×1/DHAP×1	Hper-CVAD+BMT	Alive without disease after 44 months
Chikatsu [4]	1	F	36	IV	Combination of CTX		Died of disease after 11 months
Onciu [5]	1	M	16	IV	LMB 89, weekly vinblastine, intrathecal CTX and palliative XRT		Died of disease after 24 months
	2	M	10	II	POG8719,XRT	DHAP×3	Alive without disease after 156 months
Adam [6]	1	M	35	IIA	CHOEP-21×5	Auto-BMT, CTX	Died of disease after 14 months
McMan [7]	1	M	21	IIE	CHOP×6		Alive without disease after 24 months
Colomo [8]	1	M	34	NR			Died of disease after 6 months
Ishii [9]	1	M	33	NR	CHOP	Allo-pbsct	Died of disease after 31 months
Rudzski1 [10]	1	M	48	IIIB	CHOP×3		Died of disease after 3 months
	2	M	49	IVB	CTX		Still alive
Gesk [11]	1	M	13	II	ALCL-99	CTX	Partial remission
	2	F	12	II	CTX		Alive without disease after 4 years
	3	M	16	IV	CTX	BMT	Died of disease after 12 months
Isimbald [12]	1	F	9	I	AIEOP	ICE, PVDA	Died of disease after 9 months
Bubala [13]	1	M	9	III	Used lymphoblastic lymphoma protocal then LMB89		Died of disease after 5 months
Reichard [14]	1	F	41	I	CHOP+XRT		Alive without disease after 58 months
	2	F	49	I	CHOP+XRT		Alive without disease after 22 months
	3	M	71	IV	CHOP+XRT		Died of disease after 22 months
	4	M	53	I	NR		NR
Stachurski [15]	1	M	33	IVB	CHOP×5 + intrathecal MTX		Relapse 10 months after diagnosis
Hyou Wook Lee [16]	1	F	26	IV	CHOP×6		Lost to follow up after 6 months
	2	M	35	IV	CHOP×8		Died of disease after 18 months

	3	M	24	IV	CHOP×6	IMVP-16×2	Died of disease after 17 months
Shuji Monose [17]	1	M	53	IV	High-dose Ara-C + auto-HSCT		Developed recurrent disease 4 months after CR
	2	M	41	IIE	CHOP		Achieved CR after 5 months follow up
Beltran [18]	1	M	27	IVB	EPOCH×6	Hper-CVAD	Alive without disease after 11 months
	2	F	41	IA	XRT		Alive without disease after 13 months
	3	F	13	IIB	LNH96-2002		Alive without disease after 62 months
	4	M	70	IIIB	CHOP-21×6		Alive without disease after 72 months
Roosbroeck [19]	1	M	27	IA	CHOP×4 +XRT		Alive without disease after 27 months
	2	F	33	IVA	CHOP×7		Alive without disease after 19 months
Bodwel [20]	1	M	66	IVB	CTX		Died 3 weeks after diagnosis
Takeuchi [21]	1	M	67	IIA	CHOP×6		Developed recurrent disease 6 months after CR
Ke Li [22]	1	M	44	IIE	CTX		N/R
Cerchieltil [23]	1	F	13	IIA	Intensive chemotherapy + auto-hHSCT + XRT		Relapsed 53 days post-transplant
Shi [24]	1	M	49	IIB	CHOP×6	ICE×2 + auto-HSCT + XRT	Developed recurrent disease 6 weeks post-transplant
Yin [25]	1	F	17	IIIA	CHOP×5		Alive without disease after 6 months
Francisco [26]	1	M	31	IIIAS	CHOP,Hper-CVAD	ICE×3	Died 238 days after diagnosis
d'Amore [27]	1	M	39	IIIB	CHOP	DHAP, dexa-BEAM	Died 11 months after diagnosis
Zanelli [28]	1	M	53	IIIB	CODOX-M×2, IVAC×2, high-dose BEAM, auto-HSCT + intra-thecal chemotherapy with MTX and Ara-C		Alive without disease after 35 months
Wass [29]	1	F	27	IV	CHOP×6, XRT	DHAP×2, ICE×2, Auto-HSCT, crizotinb	Died 30 days after crizotinib treatment
Chapman [30]	1	M	39	IIIA	R-CHOP		Died 6 weeks after diagnosis
This study	1	M	24	IIIA	CHOP×5	ICE×5,GEMOX+dexamethasone r+ crizotinb	Died 60 days after crizotinib treatment

Commentary: CTX: chemotherapy; MTX: methotrexate; NR: not reported; NA: not available XRT: radiation therapy; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone; PBSCT: peripheral blood stem cell transplant; ICE: ifosfamide, carboplatin, etoposide; PVDA, prednisone, vincristine, doxorubicin, asparaginase; DAHP: dexamethasone, cytarabine, cisplatin; CHOEP-21: cyclophosphamide, adriamycin, vincristine, etoposide, prednisone; BMT: bone marrow transplantation; hyperCVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with cytarabine and methotrexate; EPOCH: cyclophosphamide, vincristine, doxorubicin, etoposide and prednisone; DHAP: cisplatin, cytarabine, and dexamethasone; BEAM: carmustine, etoposide, cytarabine, and melphalan; GEMOX: gemcitabine, cisplatin.

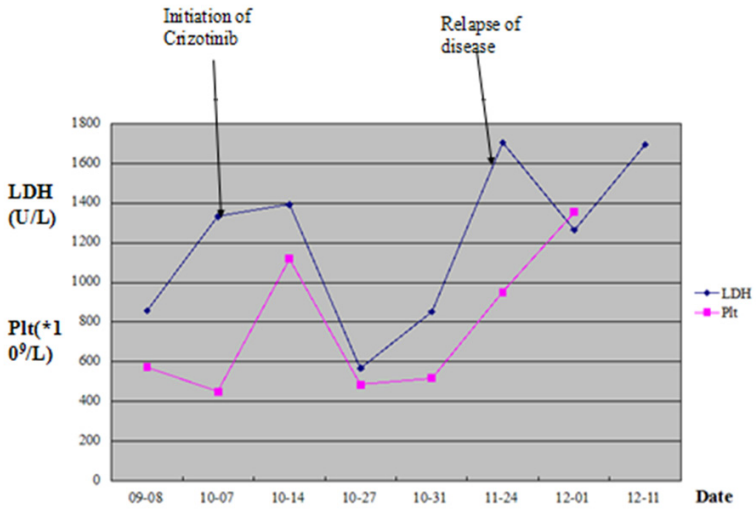

Figure 6. LDH level and platelet counts of this patient after undergoing a second relapse.

both the cytoplasm and nucleus [10, 11]. However, exceptions to this pattern have been reported; Onciu et al described a case of NPM-ALK + DLBCL case with granular expression of ALK protein only [12]. Recently, Seung et al found a rare case of RANBP2-ALK + DLBCL in which IHC demonstrated that ALK protein was located on the nuclear membrane [13]. There have been further reports of atypical localization of ALK protein that implicate additional genetic abnormalities [14-16]. In the present case we observed granular stains of ALK in the cytoplasm, suggestive of the t (2; 17) which was confirmed by RT-PCR for the *CLTC-ALK* fusion gene (**Figure 5**).

Effective treatment strategies for ALK+ DLBCL have not been investigated in detail due to the low incidence of this disease. Standard treatment regimens include combined chemotherapy, chemotherapy and radiotherapy, or radiotherapy alone. Our case was in accordance 90% of the reported cases in showing evidence of progression [3]. Case reports are suggestive of a poor prognosis associated with ALK + DLBCL, with outcome depending largely on clinical stage. The average DFS is 41 months when diagnosed at early stage while the median OS drops to 11 months when diagnosed at progression. There has been no effective protocol for the disease and combined chemotherapy is currently the main treatment despite the poor response observed in some patients. **Table 2** provides a summary of treatment programs and the outcome of all ALK + DLBCL cases reported to date. CHOP or similar protocols are the main choice and the 5-year OS was only 25%. In the present case after five courses of CHOP the patient achieved PR but soon relapsed, after which another five cycles of ICE regimen had little effect, possibly highlighting an underlying poor sensitivity to chemotherapy generally. HSCT is recommended for patients with poor prognosis, but an analysis by Beltran et al showed that seven of eight patients receiving auto-HSCT died, with OS after transplant ranging from 3 to 44 months [3]. Recently Zanelli et al reported a stage III, group B patient who survived 35 months after undergoing chemotherapy, radiotherapy and auto-HSCT [17]. Rituximab was not considered due to the absent expression of CD20 on tumor cells and an absence of supportive evidence. Amor et al detected activation of the STAT3 pathway in a SQSTM1-ALK + patient and suggested STAT3 pathway inhibitors could be targets for some cases of ALK+DLBCL with rare cytogenetic abnormalities [18]. Crizotinib is an inhibitor of tyrosine kinase receptors including ALK and CD117 and has been found to be effective against inflammatory myofibroblastic tumor or non-small cell lung cancer with ALK rearrangement [19, 20]. The FDA has approved crizotinib as a molecularly targeted agent for NSCLC with ALK rearrangement. Preclinical studies of ALK-positive DLBCL found that inhibition of ALK-activity resulted in sustained tumor regression in the xenotransplant tumor model and cell lines. These findings support a role of CLTC-ALK in the maintenance of the malignant phenotype thereby providing a rational therapeutic target for these otherwise refractory tumors [21]. Interestingly, Armstrong et al observed that different types of ALK fusion proteins produced differential effects on proliferation, transformation and invasion in vitro and in vivo. There is also evidence that different ALK fusion genes exhibit differential sensitivity to ALK inhibition [22, 23]. These trials have provided solid evidence for the application of ALK-inhibitors.

Recently Wass et al reported a relapsed ALK+ DLBCL case after crizotinib treatment, in which the patient achieved PR but relapsed quickly due to crizotinib resistance [24]. Despite the short remission time in the patient, crizotinib showed some efficacy in treating ALK + DLBCL and provided evidence for further clinical research. Although our patient demonstrated clinical improvement as a result of chemotherapy, the disease was unfortunately rapidly progressive. He was subsequently treated with two courses of GEMOX + Dexamethasone with additional ALK inhibitor crizotinib and the symptoms improved. Computer tomography revealed an improvement of lymphadenopathy and LDH levels declined transiently but symptoms deteriorated rapidly with increased LDH and platelets. The patient died two months later due to massive progressive general disease. Nevertheless, we show a partial response to this new agent. It is plausible to speculate that the sooner we use this new molecular targeted drug, the more effective it may be; it will be important to determine this in future trials.

To conclude, we diagnosed a rare case of ALK + DLBCL with spleen involvement and explored its pathology, cytogenetics, diagnosis and treatment. Due to its low incidence and non-specific morphology, ALK + DLBCL is easily misdiagnosed, with accurate identification requiring particular vigilance from physicians and pathologists. Treating this disease also remains a considerable challenge therefore the small molecule ALK inhibitor crizotinib in combination with other agents may provide a potential new therapeutic option. Further investigation in clinical trials is now warranted.

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Disclosure of conflict of interest

None.

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