



ALK positive diffuse large B-cell lymphoma, lymphoplasmablastic differentiation

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Abstract

We report detailed clinical and pathologic features of cases of anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma (ALK-DLBCL), a rare entity with only 33 currently reported cases. This reported case. Biopsies from adult male patients aged, 44 years (three lymph nodes And one skin lesion) the lymph node exhibited immunoblastic/plasmablastic morphology. By immunohistochemistry and they expressed cytoplasmic ALK-1, CD138, VS38 (3/3), monoclonal cytoplasmic light Chain, CD45, CD19, CD79 and were negative for CD3, CD30, CD20 and EMA. Showed rare CD43 (.) reactivity.

Keywords: ALK positive, difuuse large B-cell lymphoma, lymphoplasmoblastic pattern, anaplastic lymphoma

Introduction

A 44 years old male patient initially presented to King Abdulaziz Specialist hospital, Taif with Bronchopneumonia of the middle lung zone) & renal impairment. Sputum analysis showed gram positive (+ve) cocci and gram negative (-ve) bacilli with no AFB. Two months later, patient presented to KAASH with hoarseness of voice and mild dysphagia. Clinical examination showed left vocal cord paralysis. Ct scan neck showed left pyriform lesion with cervical lymphadenopathy. Bronchoscopy, esophagoscopy, and laryngoscopic biopsy were performed. Histopathology showed non-specific infection with no malignancy. A month later, patient presented with disseminated herpes zoster. Patient given. Acyclovir for 5 days and referred to Oncology Surgeon. Clinical examination showed a right outer canthus deep ulcer and wound, generalized lymphadenopathy (cervical, axilla and inguinal). Left thigh ulcerated lesion was also present. Patient was tested for HIV, II, P24 Ag in serum HCV, HBV all are negative. Again total protein in serum was high (13gm/dl) while serum albumin is low (2gm/dl). Excision biopsy of right cervical lymph node together with biopsies from right outer canthus ulcer and left thigh lesion were performed. The lymph node showed high grade ALK +ve large B-cell lymphoma with plasmablastic differentiation, skin biopsies from right canthus and left thigh showed chronic non-specific infections. Ct chest and abdomen showed nodular lung lesions involving both lungs, hepato-splenomegaly, para-aortic and Mesenteric lymph node enlargement. Patient gives history of fever and weighs loss. A staging bone marrow showed low level involvement by chronic lymphocytic leukemia, but no evidence of large cell lymphoma. The patient received CHOP and neck Irradiation for stage IV disease. Patient currently alive.

Results

Immunohistochemical result

Punnel of immuno stain are preformed showing the atypical Lymphoid cell are positive for B cell marker CD79 (Figure 1) and CD19. About 30% of the cells are positive for CD 43 and CD4. Plasma cell marker show 40% positivity with CD 138 (Figure 2) as well as VS38 (3/3). Kappa and Lamda show restriction with 100% positivity with Lamda stain. ALK antibody show strong granular cytoplasmic positivity (Figure 3). K167 is > than 80% EBV is strong positive (Figure 4). White negative result are observed with Cd20, BCL6, CD10, CD3, Cyclinc D, CD23, EMA, and CD30 (Figure 5).

Histological examination of the lymph node

The lymphoid tissue showing partial effaced architecture with vague nodular pattern accompanied by sclerosis and star sky appearance. The neoplastic infiltrate is composed of intermediate nuclei, prominent multiple nucleoli and abundant amorphelic cytoplasm, with focal area showing plasmocytoid differentiation (Figure 6). Frequent Mitotic figures are seen.

FISH for ALK gene rearrangement

FISH demonstrated an ALK gene rearrangement (Figure 7). Demonstrates a clearly separated. Orange and green signal indicating rearrangement of the ALK gene, (arrow) 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.

Discussion

We report A cases of plasmablastic lymphoma kinase positive diffuse large B-cell lymphoma (ALK-DLBCL) based on

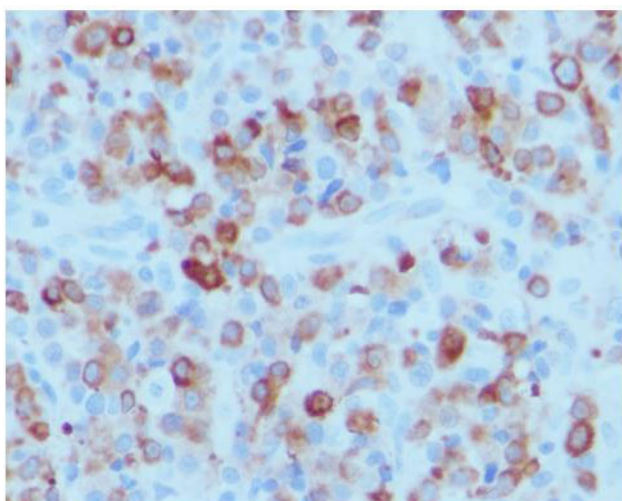


Figure 1. High power examination, original magnification x40. CD79, with a moderate and focal membrane pattern.

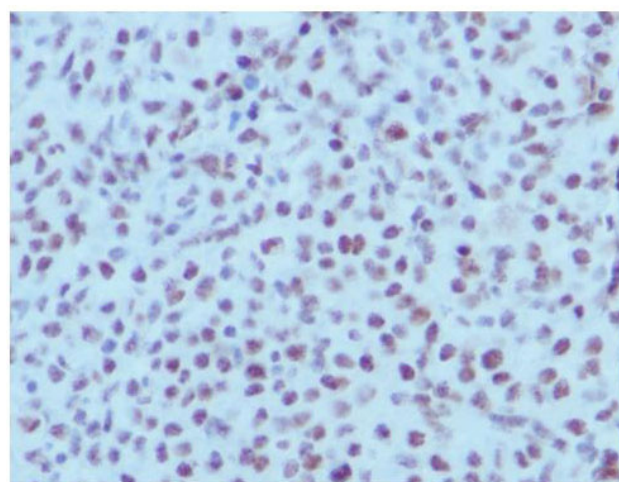


Figure 4. High power examination, original magnification x40. The tumor show focal strong nuclear stain with EBV stain.

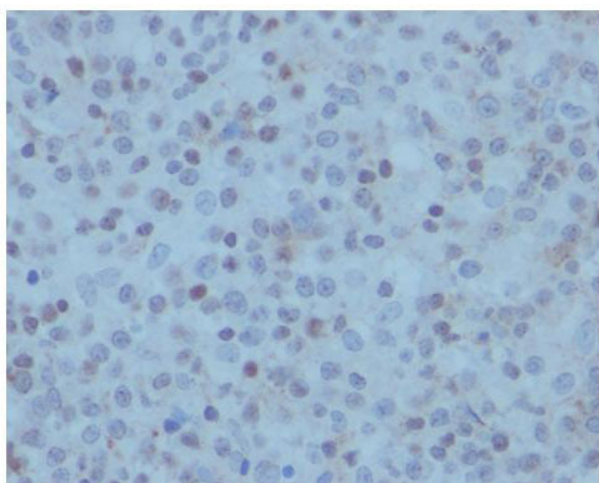


Figure 2. High power examination, original magnification x40. CD138, with weak and focal nuclear and cytoplasmic pattern.

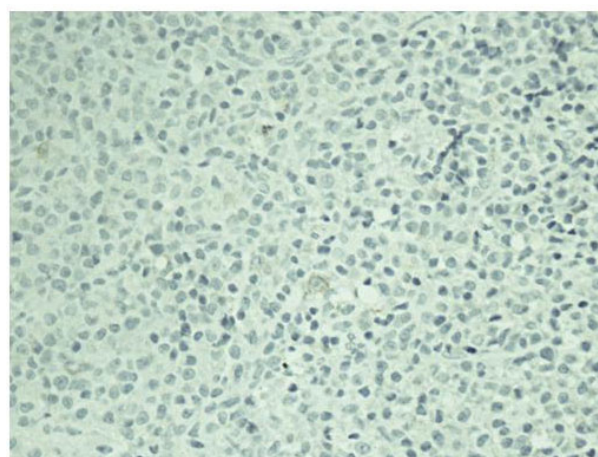


Figure 5. High power examination, original magnification x40. CD30 for the tumour cell are negative.

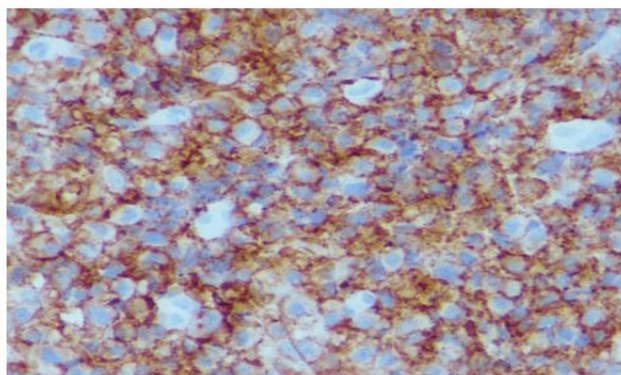


Figure 3. High power examination, original magnification x40. The cells are strongly expresses ALK, with a diffuse cytoplasmic and nuclear pattern.

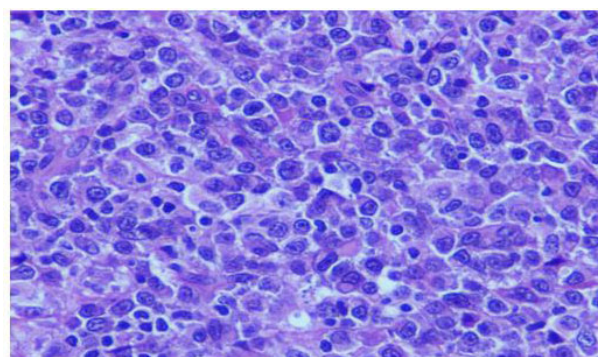


Figure 6. High power examination, original magnification x40. Morphologic features of ALK-positive large B-cell lymphoma. Characteristic plasmablastic and immunoblastic morphology (H&E staining).

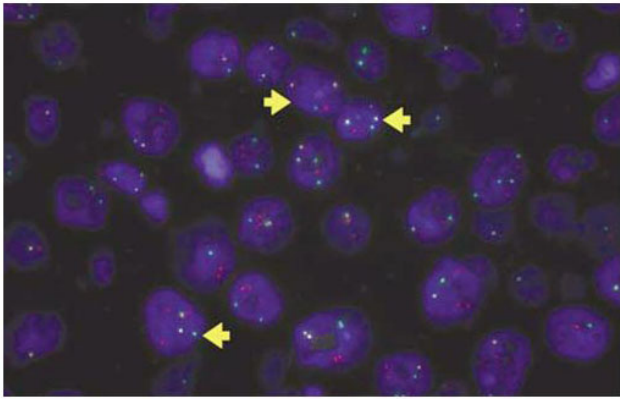


Figure 7. Fluorescence in situ hybridization (FISH) of ALKDLBCL Showing ALK gene rearrangement using the ALK break Apart probe from Vysi Inc. The FISH pattern is positive for rearrangement involving the ALK gene locus (arrows). The typical abnormal pattern would be expected to show 1R1G1F (one red and 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.

morphologic and immunophenotypic similarity to those previously described [1-6]. ALK-DLBCL was initially described by [1]. Our study of cases brings the total number of 33 reported cases of ALK-DLBCL in the literature to 34.

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. A sinusoidal growth pattern may be seen. Immunohistochemically, ALK-DLBCL shows features suggesting plasmacytic differentiation, with positivity for CD138, VS38c, and monotypic cytoplasmic light chain. The characteristic ALK staining is usually cytoplasmic and coarsely granular. Occasional cases with nuclear and cytoplasmic positivity have also been reported. CD4, and CD43 are variably positive, while CD30, B-cell related antigens (CD20), and T-cell related antigens (CD3) are negative.

Although, a fairly typical immunohistochemical (plasmacytic) profile has been established for ALK-DLBCL, it is clear that some immunophenotypic heterogeneity exists. As in some reported case in the review literature.

CD 20 highlighted rare positive tumor cells, providing a helpful clue to the underlying B cell lineage. CD20 positivity, even focal, is distinctly unusual. Also some cases been reported to show 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 [3], report one of their 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, 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 all summarized in. ALK-DLBCL (Table 1) spans 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 multi-agent lymphoma Chemotherapy and an aggressive Clinical course. 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. The recent discovery of underlying ALK rearrangement 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 (LCTC) gene on chromosome 5q35, resulting in CLTC-ALK and NPM-ALK fusion products, respectively [2-6,8-11]. Both of these rearrangements were originally identified in classic ALK (+) ALCL, with NPM-ALK being distinctly more common (70-80% of cases). 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 [5], reported on 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 [1,17] 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, this case had a conventional B-cell immunophenotype (CD97+). Was EMA (-) and CD30 negative result. ALK aberrations, specifically involving rearrangements

Table 1. Comparison of selected clinical features of the 33 reported cases of ALK-DLBCL.

Author (Reference)	Case Number	Age & Sex	Site of the disease	Stage	Therapy	Present clinical status
Delsol [1]	1	53/M	Systemic LA, splenomegaly	IVA	CTX plus relapsed, BMT	Dead of disease after 26 M
	2	15/M	NR	I	COPAD-Ara-C	Alive without disease after 156 M
	3	37/M	Mediastinal LA (2)	II (I)	M-BACOD (2)	Cases 3, 4, 7 – dead of disease after 9 M
	4	44/M	--	III-IV	B-CHOP (1)	--
	5	67/M	--	(4)	MOPP + XRT (1)	Lost to follow-up after 11 M
	6	51/M	--	--	ACVBP (2)	Alive without disease after 14 M
	7	60/M	--	--	--	See case 3
Gascoyne [2]	1	46/M	Supraclavicular and abdominal LA	III	CTX, relapse at 5 months, CTX and XRT	--
	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 M
	4	48/M	Axillary LA	1A	CTX	Alive without disease after 27 M
	5	53/M	--	--	--	--
	6	58/M	Supraclavicular involvement and-Subarachnoid involvement	IV	CHOP+ Rittuximab	Dead of disease after 6 months
De Paepe [3]	1	10/M	Cervical mass	II	ALCL-99 HR followed by SFOP-	Alive without disease after 6 M
	2	13/F	Cervical LA, HSM, mediastinal Mass (at relapse)	III	NHL-BFM ALCL99 with ALCL relapse, BMT	Dead of disease after 3 M
	3	26/M	Cervical LA, base of tongue Tumor	II	CHOP_4/vim_1/DHAP	Dead of disease after 14 M
Chikatsu [4]	1	36/F	Multiple transmuscular tumors, Bilateral ovarian tumors, HSM	IV	Combination CTX	Dead of disease after 11 M
Onciu [5]	1	16/M	Scalp and parietal bone mass, Cervical , axillary, and inguinal LA, multiple lytic skeletal lesions	IV	LMB 89, poor response	Dead of disease after 24 M
	2	10/M	Laryngeal supraglottic mass, Cervical and submandibular LA	II	POG8719, XRT and DAHP	Alive without disease after 156 M
Adam [6]	1	35/M	Right cervical and supraclavicular LA	IIA	CHOEP-	Dead of disease after 14 M
McManus [7]	1	21/M	Pyloric mass	IIE	CHOP	Alive without disease after 2 Y
Colomo [8]	1	34/M	Generalized LA	NR	Specialized NR	Dead of disease after 8 M
Ishii [9] (Abstract only)	1	33/M	Right neck LA, at relapse multiple paraaortic LA, and splenomegaly	NR	CR with chemotherapy and local XRT	Dead of disease 31 M
Rudzski [10] abstract	1	48/M	Large upper neck mass	IIIB	CHOP	Dead of disease 3 M
	2	49/M	Abdominal LA, stomach infiltrate	IVB	On chemotherapy	Currently alive
Gesk [11]	1	13/M	Cervical LA	II	ALCL99 SR: multi-agent CTX	Partial remission
	2	12/F	Mediastinal mass, cervical La	II	Multi-agent chemotherapy	Alive without disease at 4 Y
	3	16/M	Mediastinal mass, cervical LN, chest wall and left pleura involved	IV	Multi-agent chemotherapy, BMT	Dead of disease after 1 Y
Isimbaldi [12]	1	9/F	Left cervical mass	I	I AIEOP LNH 97, CR, ICE	Dead of disease after 9 M
Bubala [13]	1	9/M	Ollier disease, generalized LA	III	Multi-agent chemotherapy	Dead of disease after 5 M
	2	41/F	Cervical lymph node	I	CHOP and left neck XRT	Alive without disease at 58 M
	3	49/F	Cervical LA	I	CHOP and left neck XRT	Alive without disease at 36 M
	4	71/M	Nasopharyngeal mass	I	CHOP and left neck XRT	Dead after 22 M
	5	53/M	Left cervix LA	I	Multi-agent chemotherapy	Currently alive

of the CLTC gene, have also been identified in some cases of inflammatory myofibroblastic tumors (IMT) [18]. Thus, ALK over expression likely contributes to the pathogenesis of a Variety of otherwise unrelated neoplasms, ALK-DLBCL, ALCL, and IMT.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	EMJ	DMN	JMJ	AAS	SMA	AMM	HB
Research concept and design	✓	✓	--	✓	--	--	--
Collection and/or assembly of data	✓	✓	--	✓	--	--	--
Data analysis and interpretation	✓	✓	--	--	--	--	--
Writing the article	✓	--	--	--	--	--	--
Critical revision of the article	✓	✓	✓	--	✓	--	✓
Final approval of article	✓	✓	✓	--	✓	✓	✓
Statistical analysis	✓	✓	--	--	--	--	--

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