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Original Article

ALK Positive diffuse large B-cell lymphoma: An archival study from a regional cancer centre in South India

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ABSTRACT

Background: *Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma (ALK-positive DLBCL) is a rare subtype of DLBCL.*

Patients and Methods: *We report detailed clinical and pathologic features of five cases of Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma (ALK-DLBCL), from our archives between January 2011 and June 2016, a rare entity with only 77 reported cases in the literature. This study is the third largest of all reported series.*

Results: *In our series we noticed male predominance with male to female ratio of 3.5:1 Three of them presented with nodal disease and two with extranodal. All patients were immunocompetent and were seronegative for HIV.All cases exhibited plasmablastic morphology. By immunohistochemistry, all 5 cases lacked expression of pan-B-cell antigens CD20.CD79a and Pax5 were variable. All were CD30 negative. They consistently expressed cytoplasmic ALK-1, CD138, cytoplasmic light chain, CD45, EMA, CD4. Unlike in any other series one of our case showed association of EBV (EBER by RISH).According to the follow-up information available one expired after 15months (Case 1) and rest have either progressive disease or stable.*

Discussion and Conclusion: *ALK+DLBCL is an entity with immunoblastic or plasmablastic microscopical appearance with round nuclei, prominent single central nucleoli and moderate amounts of eosinophilic cytoplasm. It is likely that the incidence of this type of lymphoma is underestimated. The recognition of ALK-*

positive DLBCL as a distinct entity is important because most patients follow an aggressive disease course, are unlikely to respond favourably to the current standard of care (R-CHOP) for CD20-positive DLBCL. Further prospective studies are needed to optimize therapies for this entity.

Keywords: *Anaplastic lymphoma kinase, ALK, diffuse large B cell lymphoma, DLBCL.*

Background

Anaplastic lymphoma kinase (ALK) positive diffuse large B-cell lymphoma (ALK+ DLBCL) is a rare novel subtype of DLBCL recognized as a separate entity in the 2008 World Health Organization (WHO) classification of lymphoid neoplasms [(1)]. To the best of our knowledge, 77 cases have been reported to date, all of these display the morphologic and immunophenotypic features as originally described by Delsol et al [(2)]. We add 5 cases from our institution studied in the last 5 years.

ALK+ DLBCL is very rare (<1%) of all lympomas and it seems to occur more frequently in male adults (M:F ratio, 3:1) and spans all age groups (9-70 years) with amedian of 36 years [(1)].The patients are immunocompetent and usually seronegative for HIV. Although lymph nodes are consistently primarily involved in cases of ALK+ DLBCL, extranodal sites including the nasopharynx, brain, stomach, ovary may be involved [(7,9,10)].

Morphologically, the lymphoma is composed of immunoblastic or plasmablastic cells, often exhibiting a sinusoidal growth pattern. Immunohistochemical staining of the tumor cells reveals a distinct profile, with a lack of B-lineage (CD20 and CD79a) and T-lineage (CD3) markers and CD30. They show consistent expression of CD138 and CD38 (plasmacytic markers), variable expression levels of CD4 and CD57, and single light-chain cytoplasmic immunoglobulin A (IgA). Notably, all the previous studies demonstrated that lymphoma cells were strongly positive for ALK in a cytoplasmic granular staining pattern, which was differentfrom the cytoplasmic and/or nuclear pattern characteristics of the T/null anaplastic large cell lymphoma (ALCL) [(3)].

In 2003, Gascoyne et al [(4)] and De Paepe et al [(5)] described six and three cases, respectively, of ALK+ DLBCL. They were characterized by t(2;17)(p23;q23), which results in the fusion of the ALK gene at chromosome band 2p23 and the Clathrin gene (CLTC) at 17q2. The usual chromosome translocation at t (2;5) (p23;q35), which is frequently associated with ALCL, and a cryptic insertion of the ALK gene into chromosome 4 at band 4q22-24 fusion is seen in few cases of ALK+ DLBCL [(6–8)].

We present detailed clinical and pathological features of 5 cases from our archives between January 2011 and June 2016. Clinically ALK positive DLBCL shows aggressive course with high relapse rates and lack of response to the standard regimens. It is a diagnostic challenge particularly when the presentation of the mass is at unusual sites; hence a high grade of suspicion is necessary to diagnose this entity.

Materials and Methods

Five cases of ALK+ DLBCL were identified from the archival material from the Department of Pathology, Kidwai Memorial Institute of Oncology from January 2011to June2016. Clinical and laboratory information was obtained from the clinical caserecords. Hematoxylin and eosin(H&E) staining and IHC analysis was conducted at department of pathology, and the HIV/HCV status was determined by department of Microbiology, Kidwai memorial institute. The hematoxylin and eosin (H&E) stained sections were prepared from formalin fixed paraffin blocks. Immunohistoc-hemical analyses included a large panel of monoclonal antibodies including LCA, CD20, CD79a, pax5, kappa, lambda, Bcl-6, CD3, CD4, CD5, CD30, CD15, LMP1, CD138 and epithelial membrane antigen (EMA) antigens. The detection of ALK protein was performed on paraffin sections fixed in buffered formalin using monoclonal antibodies. Table 2 & Table 3 provide the summary of the immunohistochemical features and the details of the antibody.Detection of

association with EBV infection was performed by RISH for EBER. When the differential diagnosis was non lymphomatous condition, depending on the site of the lesion, GFAP, PLAP, CD117, S-100, synaptophysin and chromogranin were done. All the H&E and IHC slides were reviewed.

Case Reports

A summary of the clinical features of the five patients is provided in Table 1.

Case 1

A 17 year old male patient presented with abdominal pain for past 1 year which had increased since past two months. On clinical examination, a mass of 8 x 8 cm was felt in the suprapubic region. CT evaluation showed mesentric lymph node enlargement and nodular lesions in the lesser sac, paraaortic and portacaval region. On fine needle aspiration, provisional diagnosis of metastatic germ cell tumor was offered. Biopsy of mesenteric lymph node showed diffuse lymphoma with immunoblastic morphology. On IHC the cells expressed ALK, EMA, CD79a, CD4, kappa, MUM1, focally positive for pax5 and negative for CD3, CD20, MPO, CD138 and CK. A staging bone marrow aspiration was negative. LDH was elevated (1168IU/L) .Patient was staged as stage III AE and was treated 4 cycles of CHOP + ICE. Follow-up scan showed progressive disease. Patient died after 15 months from the date of diagnosis.

Case 2

65 year old male presented with the swelling on the right side of neck for 3 months and fever for 2 months. An excisional biopsy of the right cervical lymph node was performed. FNAC of lymph node was done and metastatic carcinoma was considered. Histopathological evaluation revealed diffuse lymphoma with plasmablastic morphology. IHC was positive for LCA, ALK, CD138,EMA, CD4, MUM 1 and kappa and negative for CK, CD20, CD3, CD30 and CD10. Staging bone marrow was negative for involvement by lymphoma. Patient was staged as stage IIIb disease and received 6 cycles of CHOP regimen. Since the patient showed partial response, the therapy was continued for additional two cycles. Follow up scan showed stable disease. At 11 months, patient is alive with stable disease.

Case 3

A 22 year old male had swelling of scalp for 9 months. Craniotomy was done elsewhere and the patient was diagnosed to have anaplastic glioma, parietal lobe. Two months post craniotomy the patient developed swelling at the same site again along with multiple new swellings and started developing weakness in the limbs. Patient was referred to a neuro-tertiary care centre for further treatment,where patient was found to have CNS lymphoma and was referred to our hospital for further treatment. Workup of the patient with whole body CT and MRI showed well defined lesions in the segment VIII of the liver suggestive of extensive disease. H&E slides were reviewed which showed diffuse sheets of neoplastic cells with plasmablastic morphology. IHC was positive for ALK, MUM 1, Pax5, BCL6 and CD138, focally positive for CD79a and negative for GFAP, CD20, EBV, LMP,CD3, CD30 and CD10. A staging bone marrow aspiration and biopsy was positive for involvement by lymphoma. Patient was staged as IV and underwent 6 cycles of CHOP with triple intrathecal therapy. At 12 months, patient is alive with stable disease.

Case 4

A 20 year old female presented with swelling in the right neck with matted level II/III/IV/V cervical lymph nodes. FNAC was done and was suggestive of large cell lymphoma. Biopsy of the nodes showed malignant lymphoma with immunoblastic morphology. IHC was positive for ALK, CD138, CD4, MUM1 and negative for CK, CD20, CD79a, CD30 and Pax5. Ki 67 was 80%. Staging bone marrow aspiration and biopsy was positive. Patient was staged IVB and is on 2nd cycle of CHOP regimen.

Case 5

A 10 year old child presented with difficulty in breathing and hoarseness of voice for a period of 6 months. Laryngoscopic examination showed a

slough covered mass in the supraglottis, true and false vocal cords and ventricle with moderate airway obstruction. FNAC was not feasible and biopsy of larynx was performed. A diagnosis of squamous cell carcinoma/malignant round cell tumor was suggested elsewhere. IHC showed positive staining for LCA, EMA, CD138, Mum1, CD4 and negative staining for CD20, Pax5, CD79a, CD3, LMP1. Staging bone marrow aspiration was negative. Patient was staged IA and treated with MCP 842 protocol. Follow-up CT scan neck showed 2x1.5 cm mass in the larynx and subcentimetre cervical lymphnodes on both sides. At 10 and 16 months PET scan showed no residual disease. At 53 months, patient is alive and free of the disease.

Results

Clinical, Histology and Immunohistochemistry findings

The details of all 5 cases included in the study are described in Table 1. The median age was 26.8 years, and there was a clear male predominance (4:1). Four of five patients were of age <25yrs. Three of them presented with nodal disease (2 cervical and 1 mesenteric LN) and two with extranodal (1 Central nervous system and 1 larynx).All patients were immunocompetent and were seronegative for HIV.

The morphologic findings in all 5 cases were more are less similar. The distinct sinusoidal growth pattern was observed in one case (case 4). There was a diffuse proliferation of tumor cells with a mixture of large immunoblasts and numerous plasmablastic cells (figure 1). Plasmablastic cells were defined as having eccentric nuclei, amphophilic cytoplasm, prominent Golgi zones. Case 4 was characterized by immunoblastic morphology with bizarre multinucleated tumor giant cells raising a suspicion of metastatic germ cell tumor, but this was not a feature in the other cases. No hallmark cells, which are seen in ALCL were present.

The immunophenotypic results in all 5 cases were more or less similar. All 5 cases lacked expression of pan-B-cell antigens CD20 and CD79a (patchy in two cases). Pax5 was positive in one case while another case showed focal positivity.CD138 was strongly positive in all cases, as was EMA (100%). Two cases showed light-chain restriction with expression of kappa. CD30 was negative in all 5 cases, highlighting the distinction from ALCL. Weak focal expression of CD4 was seen in 4 cases, but CD3 was negative in all cases. The pattern of ALK expression was identical in all 4 cases with one exception (Case no 2) which showed agranular positivity with golgi accentuation (figure- 3) . In rest of them ALK protein expression was restricted to the cytoplasm and showed a fine granular pattern in all cells (figure 2). Ki-67 proliferating index was high in all the cases ranging from 50% to 80%

EBERISH was positive in only one of our case (Case 3). Tumor cells showed EBV localization with in situ hybridization (EBERISH) (figure 3). However earlier studies lack viral participation in ALK+ DLBCL and is in contrast to the other variants of DLBCL with plasmacytic differentiation, such as primary effusion lymphoma and plasmablastic lymphoma [11,12].

Therapy details

Four of the five patients had advanced-stage disease at diagnosis with bone marrow involvement in two cases. According to the follow-up information available one expired after 15months (Case 1) and rest have either progressive disease or stable. One paediatric patient (Case 5) presented in stage I. Two presented in stage III and two in stage IV. The child with laryngeal involvement (case 5) was treated with MCP842 protocol like in high grade lymphoma. The rest were treated with cyclophosphamide + adriamycin + vincristine + prednisone (CHOP) chemotherapy and additional ICE for case 1 as he did not respond and the disease progressed. However he succumbed. None of them were administered rituximab with CHOP.

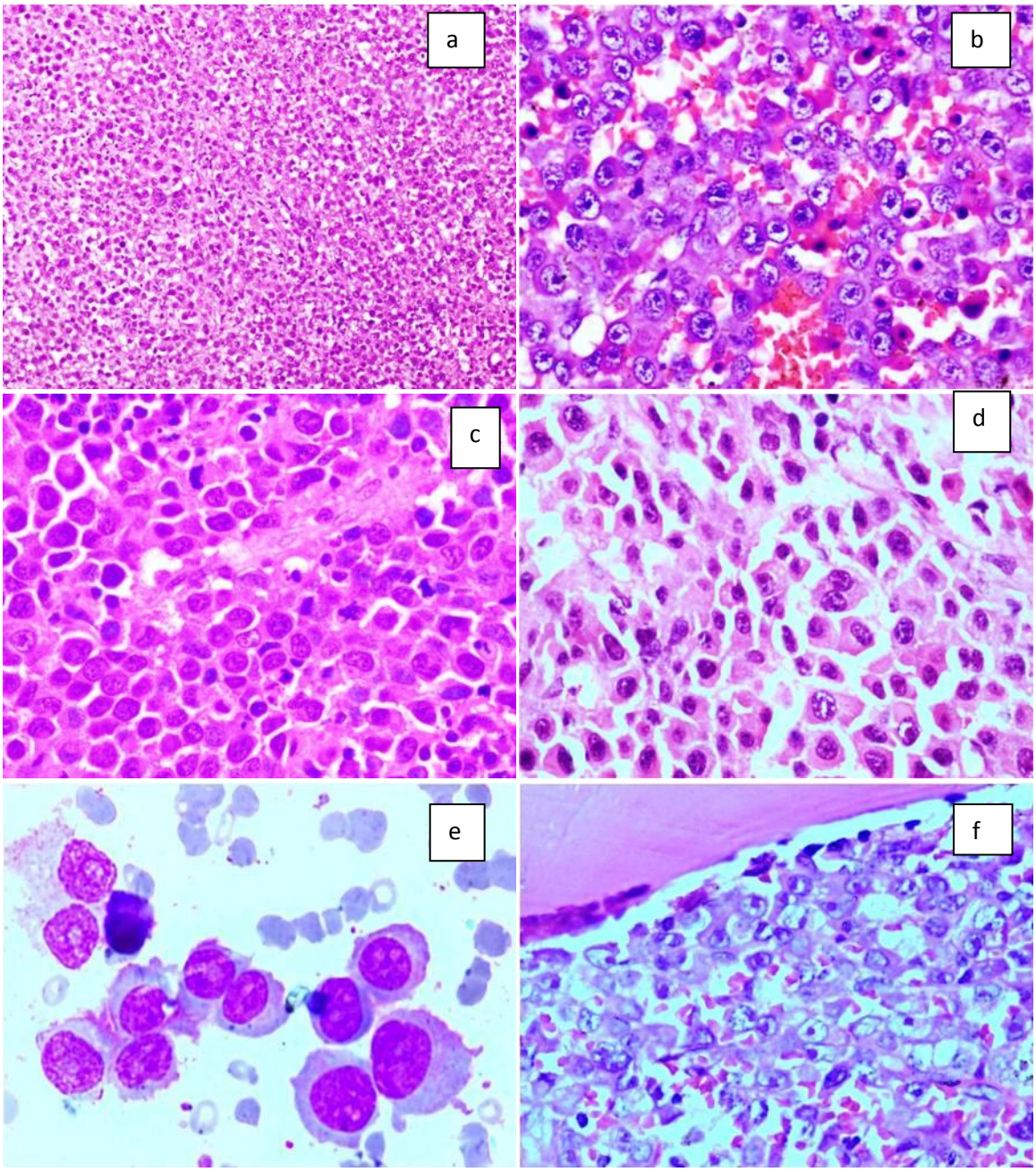

Figure 1: Architectural and cytological features of ALK- positive DLBCL.(a) Diffuse proliferation of large cells (b) large cells with round regular nuclei, single central eosinophilic nucleoli, dispersed chromatin depicting immunoblastic morphology(c) sinusoidal infiltration(d)plasmablastic morphology(e) Plasmacytoid cells infiltrating the bone marrow(case 3)(f)BM biopsy showing infiltration of cells (case3)

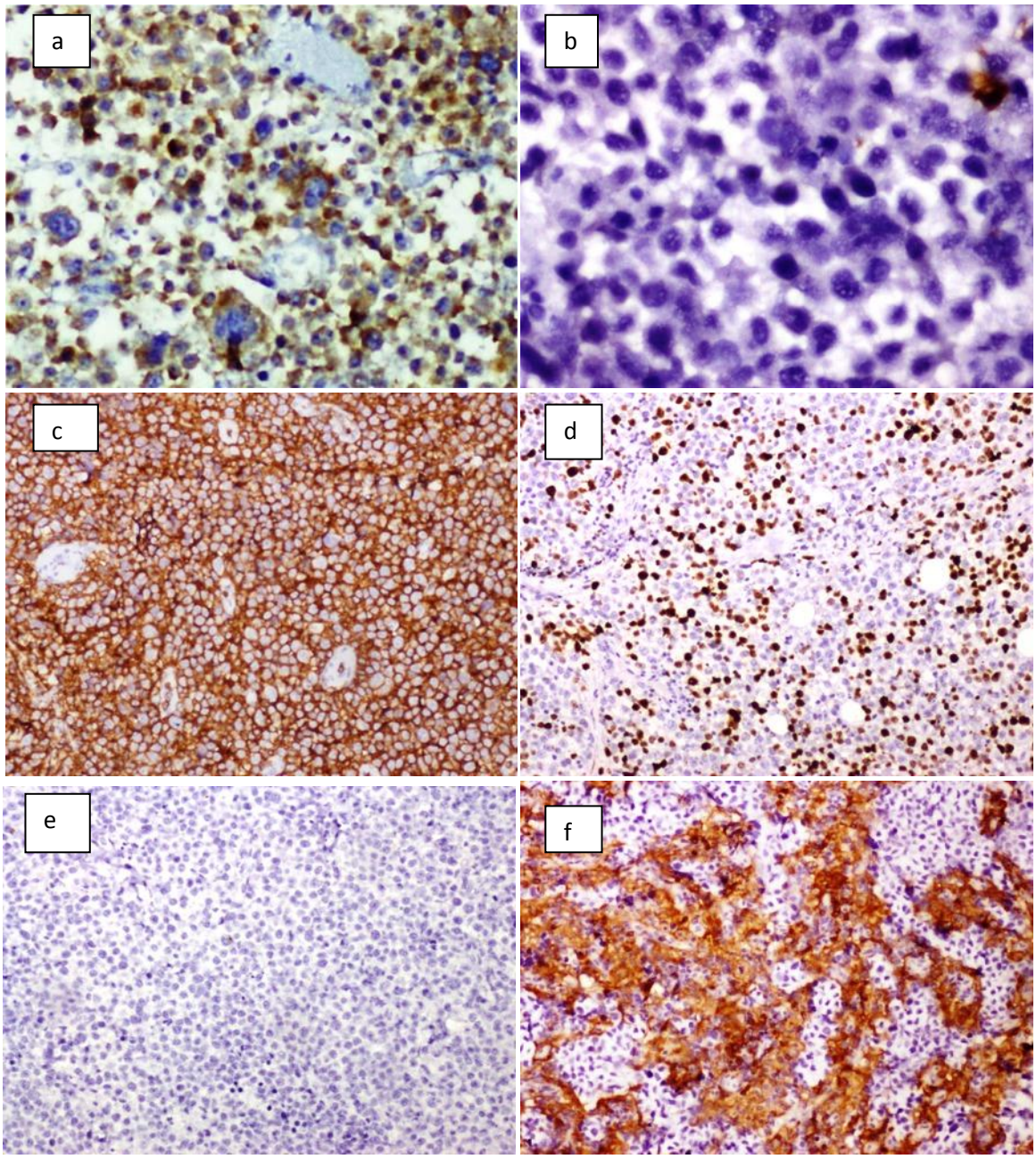

Figure 2: immunohistochemical profile of ALK-positive DLBCL(a) characteristic granular cytoplasmic expression of ALK(b)negative for CD20 (c)stong positivity for CD138(d) expression of MUM1 (e)lack of expression of CD30(f) expression of EMA

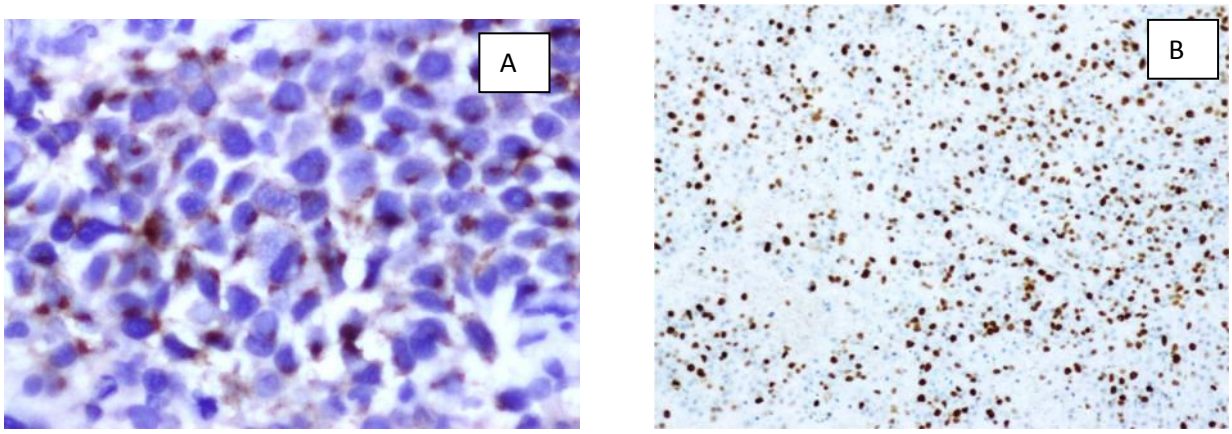

Figure 3: (A) expression of ALK with characteristic golgi accentuation in case 2(B) expression of EBER by RISH in case3

Table 1: Clinical characteristics of reported cases

Case	Age	Sex	Primary Site	Bone marrow involvement	Stage	IPI	Treatment	Survival (months)	Outcome
1	17	M	Mesentric Lymph node	No	IIIAE	1	4 cycles of CHOP + ICE	15	Expired
2	65	M	Cervical node	No	IIIB	2	CHOP-6 cycles Additional 2 cycles after partial response	11	Alive, Stable disease
3	22	M	Brain (parietal lobe)	Yes	IV	3	CHOP 6 cycles with triple IT	12	Alive, Stable disease
4	20	F	Cervical node	Yes	IVB	2	CHOP	5	2nd chemo to be started
5	10	M	Larynx	No	IA	1	MCP 842 protocol	53	Alive, Stable disease

Table-2 Morphology and Immunohistochemistry of the reported cases

Cases/ IHC	1	2	3	4	5
Morphology	Immunoblastic	Plasmablastic	Plasmablastic	Immunoblastic	Plasmablastic
ALK	+	+(with golgi accentuation)	+	+	+
LCA	+	+	+	+	+
CD20	-	-	-	-	-
CD3	-	-	-	-	-
CD79a	+	-	Focally +	-	-
Pax5	Focally +	-	+	-	-
CD4	NA	+	+	+	+
CD10	-	-	-	-	-
CD30	-	-	-	-	-
CD138	-	+	+	+	+
Mum 1	+	+	+	+	+
EMA	+	+	+	+	+
Kappa	+	+	NA	NA	NA
CK	-	-	-	-	-
Ki67	70%	65%	80%	80%	50%
EBERISH	Negative	Negative	Positive	Negative	Negative

Table-3 Antibody clone, make and dilution details used for the study

Antibody	Clone/make	Dilution	Species
ALK	SP8/Biogenex	1:40	Rabbit
LCA	LCA88/Biogenex	1:100	Mouse
CD20	L26/Biogenex	1:70	Mouse
CD3	PS1/Biogenex	1:70	Mouse
CD79a	11E3-2/Biogenex	1:70	Mouse
Pax5	ZP007/Biogenex	1:50	Mouse
CD4	4B12/Biogenex	1:60	Mouse
CD10	56C6/Biogenex	1:60	Mouse
CD30	HRS-4/Biogenex	1:70	Mouse
CD138	MI14/Biogenex	1:60	Mouse
MUM1	EAU32/Biocase	1:60	Mouse
EMA	E29/Biogenex	1:100	Mouse
Kappa	LIC1/Biogenex	1:80	Mouse
Lambda	HP6054/Biogenex	1:100	Mouse
CK	C11/Biogenex	1:100	Mouse
BCL6	LN22/ Biocase	1:100	Mouse
Ki67	BGX-297/Biogenex	1:40	Mouse

Discussion

Among 77 cases reviewed by Beltran, the mean age was 37 years, and 14 patients (20%) were younger than 20 years. We had 80% (4/5) younger than 25 years. Male predominance was seen .We

noticed male predominance with male to female ratio of 3.5:1 which is similar to other reports.

53% of patients presented exclusively with nodal disease and 22% of them had cervical lymph node involvement. Of the remaining 47% of patients, the most common extranodal sites were bone marrow(15%), bone(11%),liver/spleen(11%) and ovary. 15% had exclusively extranodal disease. In our case series three out of two had nodal presentation with two of them presenting as cervical enlargement. Other two had extranodal involvement, one in brain and the other in larynx.

We report five cases of anaplastic lymphoma kinasepositive diffuse large B-cell lymphoma (ALK+DLBCL) based on morphologic and immunophenotypic similarity to those previously described(1, 4-7). ALK+DLBCL was initially described by Delsol et al in 1997 [(1)]. ALK+DLBCL is an entity with immunoblastic or plasmablastic microscopical appearance with round nuclei, prominent single central nucleoli and moderate amounts of eosinophilic cytoplasm. DLBCL with plasmablastic features and terminal B-cell differentiation represents a heterogeneous spectrum of distinct entities [(13)].

Differential diagnosis of ALK+DLBCL should include lymphoblastic lymphoma, anaplastic and immunoblastic variants of DLBCL, plasmablastic lymphoma (PBL), primary effusion lymphoma (PEL), and plasmablastic myeloma. Lymphoblastic lymphoma show characteristic Tdt positivity which is lacking in the ALK +DLBCL. Immunoblastic and anaplastic DLBCL can be excluded on the basis of the characteristic immunophenotypic pattern of CD20 positivity and other characteristic B cell markers being positive. PBL is distinguished from ALK-positive DLBCL by its lack of expression of the ALK protein and frequent association of immunosuppression, commonly HIV. Detection of paraproteinemia in blood and/or excess light chains (Bence Jones proteins) in urine, lytic bone lesions, and hypercalcemia or anemia favors the diagnosis of plasmablastic myeloma. PEL show characteristic association with HHV8 coinfection. The diagnosis of ALK+DLBCL can be complicated by its morphologic resemblance to myeloid malignancies particularly extramedullary myeloid tumor which can be excluded by immunohisto-chemical studies of myeloid markers. ALK-positive ALCL, although a T-cell lymphoma, should be considered in the differential diagnosis of ALK+DLBCL given its good prognosis [(14)].

ALK+ DLBCL can be a great mimicker of non lympho-haematopoietic tumor. Three of our cases were diagnosed initially as germ cell tumor, metastatic carcinoma and high grade glioma on morphology. So a high suspicionaided with battery of immunohistochemical markers are necessary to arrive at the diagnosis.

The most commonly observed ALK staining pattern was cytoplasmic and granular, caused by clathrin-ALK fusion.This pattern is explained by the function of clathrin, which is present in coated vesicles necessary for at least 50% of the endocytic activity of the cell [15,16]. In contrast, the NPM-ALK fusion protein seen in ALCL has a characteristic nuclear and cytoplasmic sub-cellular localization pattern, which was found in a few cases. The gene NPM1, which codes for nucleophosmin, is frequently overexpressed and rearranged in human cancer and has proto-oncogenic and tumor suppressor features [17]. All our cases showed cytoplasmic granular positivity for ALK, one with Golgi accentuation.

ALK+ DLBCL shows 100% plasmacytic differentiation with expression of MUM 1 and EMA. This support the inference that it is derived from post germinal B cell lymphocytes. Based on these findings, ALK+DLBCL falls into the category of non-germinal centre DLBCL. Patients with DLBCL of non-germinal centre immunhistochemical profile have worse clinical outcomes than their counterparts of germinal centre -like origin [18-20].

Four of five of cases had advanced disease with two of them presenting with bone marrow involvement. The clinical stage has a correlation with overall survival (OS). Our case with stage I did show good OS with disease in remission at the

end of 53 months.In paediatric group, aggressive regimens such as ALL like regimens were instilled while in adults CHOP or CHOP like regime was opted. Our paediatric patient was treated with MCP842 and doing well after 53 months and is disease free.

The International Prognostic Index (IPI) score has been the most widely used risk-stratifying toolin aggressive non-Hodgkin lymphoma (NHL).The IPI score relies on five clinical factors (age, performance status,lactate dehydrogenase levels, extranodal involvement, and clinical stage) to classify patients as high, high–intermediate, low–intermediate, and low risk. Unfortunately, the IPI scorewas available in a minority of the patients with ALK-positive DLBCL (12%) [21]. However, as the IPI score has been proven tobe predictive in other aggressive histological variants of NHLsuch as HIV-associated DLBCL [22] and peripheral T-celllymphomas (PTCL) [23], one can infer that it would also be ofvalue in ALK-positive DLBCL. Among our patients conclusion could not be drawn with the stage and IPI score, as the number was small.

Conclusions

To conclude, ALK-positive DLBCL is an aggressive form of DLBCL with ectopic ALK expression due to CLTC-ALK gene rearrangement in most patients. Although this subtype of lymphoma is a recognized entity from WHO 2008, its identification in routine pathology laboratories can be challenging, especially distinguishing among plasmablastic lymphoma, immunoblastic DLBCL, ALCL of T-null cell lineage, and poorly differentiated/anaplastic carcinoma. It is likely that the incidence of this type of lymphoma is underestimated. The recognition of ALK-positive DLBCL as a distinct entity is important because most patients follow an aggressive disease course, are unlikely to respond favorably to the current standard of care (R-CHOP) for CD20-positive DLBCL. They could be candidates for novel treatment approaches. They can be easily mistaken to have nonhematopoietic malignancies, which results in delayed diagnoses and inappropriate therapy. This report of the largest case series to date from South India is to create awareness of this uncommon lymphoma, benefiting pathologists, hematologists, medical oncologists and patients alike.

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