

CASE REPORT

OPEN ACCESS

Full open access to this and thousands of other papers at <http://www.la-press.com>.

ALK-Positive Large B Cell Lymphoma—Unusual Subtype of Diffuse Large B Cell Lymphoma (DLBCL)

Pramod Nath, S. Bhattacharya and Reena Bharadwaj

Department of Pathology, Army Hospital (R & R), Delhi Cantt-110010, India. Email: peanuts_6703@yahoo.co.in

Abstract: Anaplastic lymphoma kinase positive diffuse large B-cell lymphoma (ALK-DLBCL) is a rare lymphoma and has been included as a separate entity in the latest WHO classification (2008) of Non-Hodgkin's lymphomas. We report a case of 65-year-old male patient who presented with multiple subcutaneous nodules on abdominal wall. Histomorphology and Immunohistochemical profile was consistent with that of ALK-positive diffuse large B cell Lymphoma. Anaplastic lymphoma kinase (ALK) staining was cytoplasmic granular staining pattern highly indicative of expression of Clathrin gene (CLTC-ALK protein). CD 20 was strongly expressed in this case which was an unusual finding as this has been reported in only a few cases which have been published. Our patient also responded well to rituximab therapy which is not administered as these are usually CD 20 negative. The case is reported for its rarity and to make the clinicians aware of this entity so that these cases may be diagnosed early and treated aggressively.

Keywords: Non-Hodgkin's lymphoma, Anaplastic lymphoma kinase, CD 20, Rituximab

Lymphoma and Chronic Lymphocytic Leukemias 2010:2 1–5

This article is available from <http://www.la-press.com>.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.

Introduction

ALK positive large B cell lymphoma (ALK-Positive LBCL) is a neoplasm of ALK-positive monomorphic large immunoblast-like B cells, sometimes with plasmablastic differentiation.¹ It is a rare type of Non Hodgkin's lymphoma (<1% of DLBCL) with less than 40 cases reported and spans all age groups (9–70 years) with a male preponderance (M:F ratio 3:1).²

It mainly involves the lymph nodes and commonly presents as a mediastinal mass. Extra nodal sites of presentation like nasopharynx, tongue, stomach, bone and soft tissue have been reported.^{2,3}

We present an unusual case of ALK-positive large B cell lymphoma which presented as skin nodules on the anterior abdominal wall.

Case Report

65 year old patient was referred to our hospital as suspected case of plasmacytoma. Patient had presented with a history of backache of five months duration, progressive in nature and radiating to both limbs. He was diagnosed as a case of prolapsed intervertebral disc (PIVD LV5-S1) with cauda equina syndrome and operated. Histopathology of soft tissue and disc material showed scattered mature plasma cell and some atypical large cells resembling plasmablasts. Patient was given a provisional diagnosis of Plasmacytoma and referred to our centre for further management.

On general examination patient was observed to be having multiple subcutaneous nodules on the anterior abdominal wall. Fine needle aspiration cytology (FNAC) of these lesions (Fig. 1) showed highly cellular smears with sheets of monotonous population of cells having high nucleo-cytoplasmic ratio (N:C ratio), bizarre pleomorphic hyperchromatic nuclei and prominent and large 1–3 nucleoli. Numerous scattered cyst macrophages and lymphoglandular bodies were also seen and a provisional diagnosis of high grade non hodgkin's lymphoma was given. Bone marrow biopsy (Fig. 2) showed infiltration by clusters of similar atypical neoplastic cells having high N:C ratio and bizarre nuclei with prominent nucleoli.

Computer tomography (CT) scan abdomen (Fig. 3) and pelvis showed multiple lymph node masses in para-aortic, aorto-caval, mesenteric and peripancreatic region. Spleen showed multiple hypo dense

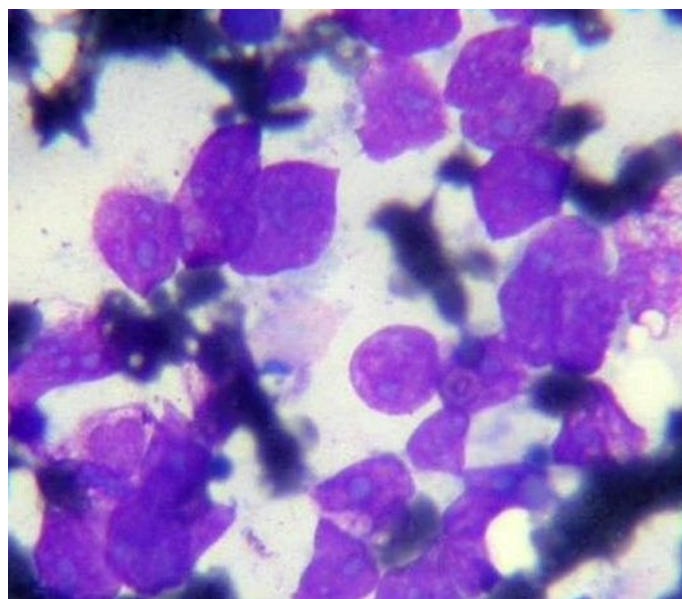


Figure 1. FNAC smears (x400) showing bizarre lymphoid cells having pleomorphic nuclei with large and prominent nucleoli.

lesions of varying size largest measuring 3.4×3.2 cm and right kidney and left adrenal also showed well defined small lesions. Enlarged common iliac and external iliac nodes and multiple soft tissue nodular deposits in subcutaneous tissue of anterior abdominal wall were also present. Biochemical parameter which were noted to be abnormal were lactate dehydrogenase (LDH) 2865 U/L (N:230–460 U/L) and blood urea nitrogen (BUN) 26 mg/dl (N:7–19 mg/dl).

Biopsy of Nodular lesion anterior abdominal wall was done for further confirmation and classification

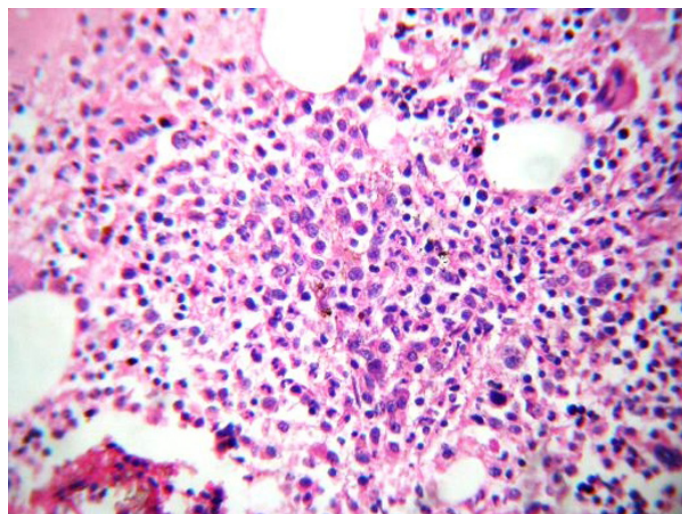


Figure 2. Bone marrow (x200) infiltrated by neoplastic cells.

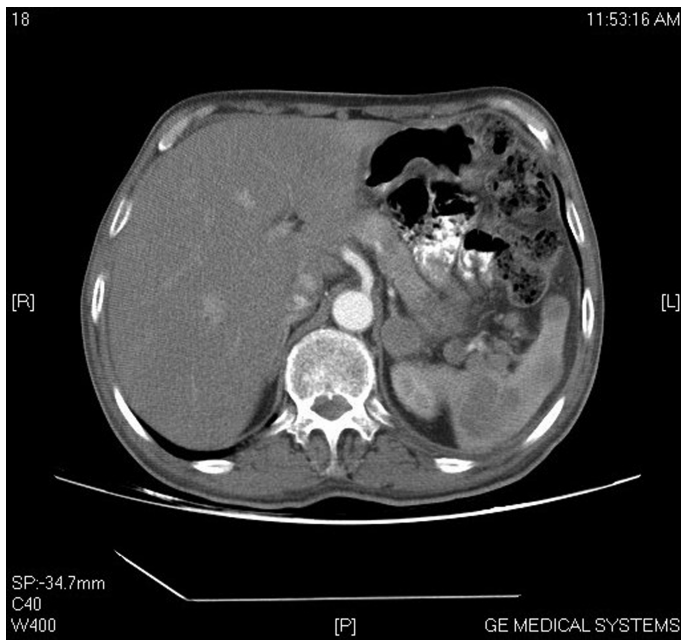


Figure 3. CT scan Abdomen showing enlarged lymph nodes and splenic lesions.

of high grade Non-Hodgkin's lymphoma. Biopsy (Fig. 4) showed monomorphic population of large immunoblast like cells with round pale nuclei having large central nucleoli. Atypical multinucleate neoplastic giant cells, numerous scattered atypical mitotic figures and foci of necrosis were present.

Immunohistochemistry showed tumor cells to be LCA negative and strongly positive for CD 20 (Fig. 5). CD 30 was negative and EMA showed focal

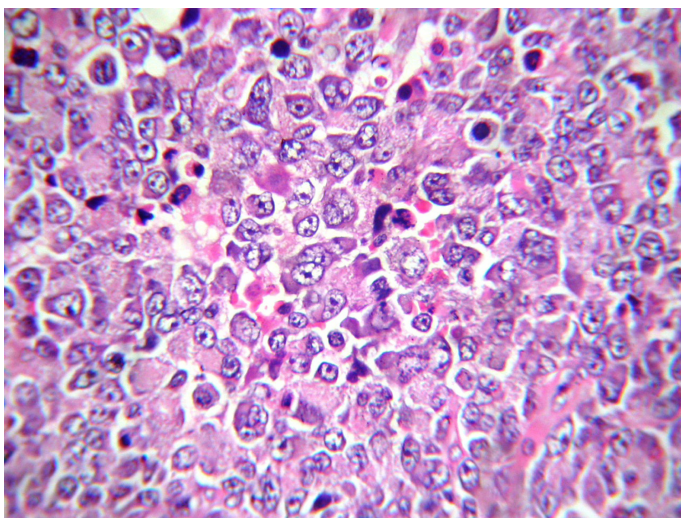


Figure 4. Haematoxylin and eosin staining (x400) showing monomorphic population of large immunoblast like cells with round pale nuclei having large central nucleoli.

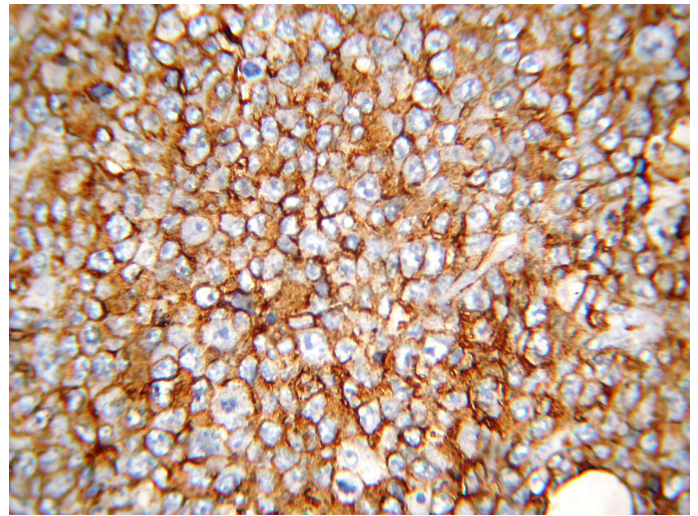


Figure 5. Immunohistochemistry: Strong CD 20 staining of tumour cells.

positivity. ALK protein expression was a strong granular cytoplasm staining of tumour cells (Fig. 6). CD 5 and CD 45RO were expressed on scattered reactive T cells and were negative in tumor cells. Lambda light chain restriction and focal IgA heavy chain expression were noted. CD 138 showed weak positivity and bcl-2 was negative.

A diagnosis of ALK-positive diffuse large B cell lymphoma with Bone marrow involvement was made based on histopathological and immunohistochemical profile. Patient was placed on rituximab, cyclophosphamide, hydroxydaunomycin, vincristine and prednisone (R-CHOP) based chemotherapy. He was

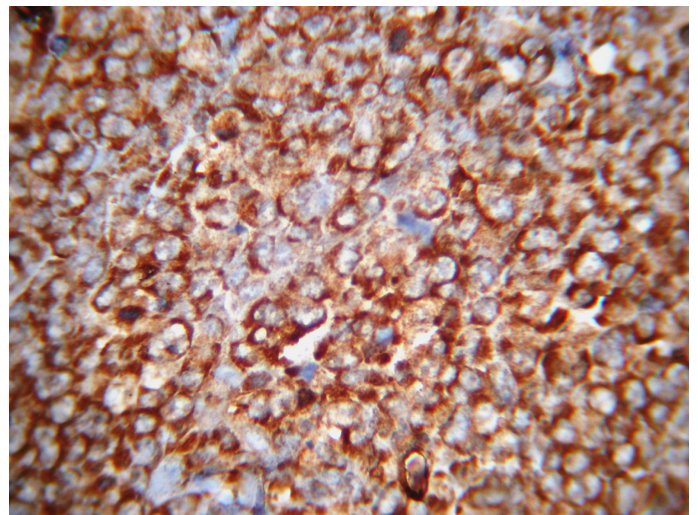


Figure 6. Immunohistochemistry: ALK protein expression -Strong granular cytoplasm staining of tumour cells.



administered eight cycles over a period of six months. Patient responded well to R-CHOP based chemotherapy and is presently in remission.

Discussion

ALK positive DLBCL is a neoplasm of ALK-positive monomorphic large immunoblast-like B cells, sometimes with plasmablastic differentiation. Histologically in our case distinct sinusoidal growth pattern of large immunoblast type cells was seen (Fig. 4) and as in other studies^{3,5} no hall mark cells typical of T cell or null cell ALCL were present.

The tumour generally shows weak or negative expression of CD 45 and CD 30 is usually negative.⁵ Focal and weak staining of CD 30 has been reported in a few cases.⁶ The tumor is also negative for CD 20.¹ ALK staining is a restricted cytoplasmic granular staining pattern highly indicative of expression of Clathrin gene (CLTC-ALK protein).^{1,3} In our case CD 45 was not expressed in tumour cells but CD 20 was strongly expressed, which was an unusual finding. A low rate of CD 20 and CD 79a expression to the tune of 11% and 18% respectively has been reported⁷ however a single study has also reported a high percentage of CD 20 positivity (four out of a total of five cases were CD 20 positive).⁸ Strong granular cytoplasmic ALK staining pattern was seen in tumour cells. The most commonly observed ALK staining pattern is cytoplasmic and granular, caused by clathrin-ALK fusion. This pattern is explained by function of clathrin, which is present in coated vesicles necessary for at least 50% of the endocytic activity of the cell.⁷

Most of these tumors being CD 20 negative are insensitive to rituximab.¹ Rituximab was added to CHOP regime of chemotherapy in our case as it was CD 20 positive. Rituximab should be used in CD 20-expressing ALK-DLBCL cases.⁸

Expression of ALK protein by lymphoid cells and description of anaplastic lymphoma kinase (ALK) translocation have typically been restricted to cases of T cell and null cell anaplastic large cell lymphoma (ALCL).³ The most frequent ALK gene rearrangement seen is clathrin-ALK in 75% of cases; however 17% corresponded to NPM-ALK fusion. ALK gene is located on chromosome 2p23 and encodes a tyrosine kinase receptor belonging to the insulin receptor superfamily, which is normally silent in lymphoid cells and it can be translocated to either the clathrin

gene locus located on chromosome 17q23 or to the NPM1 gene located on chromosome 5q35, constituting the clathrin-ALK and NPM-ALK fusion products respectively. All ALK fusion proteins share two essential characteristics: 1) presence of an N-terminal partner protein, a gene promoter which controls aberrant transcription of ALK chimeric mRNA and the expression of its encoded fusion protein, and 2) presence of an oligomerization domain in the sequence of the ALK fusion partner protein which mediate constitutive self association of the ALK fusion causing constant ALK domain activation. Oncogenesis occurs from ensuing dimerization leading to constitutive activation of ALK tyrosine kinase activity.⁷ Stachurski and colleagues⁶ described a novel mechanism of ALK activation by means of a cryptic 3' ALK gene insertion into chromosome 4q22–24. The role of this anomaly in lymphomagenesis is unclear.

ALK-DLBCL is a distinct subtype of DLBCL with large immunoblast like B cells with sometimes plasmacytic differentiation that affects pediatric and adult patients. It has characteristic genetic abnormalities and corresponding specific ALK-staining patterns with a prognosis that depends largely on clinical stage. The clinical course of ALK-DLBCL is aggressive with primary refractory disease and high relapse rates. The classical CHOP regimen appears insufficient to treat this condition and newer, more intensive therapies are needed. Given its CD 20-negativity, the role of rituximab in the treatment of ALK-DLBCL is unclear. Despite this aggressiveness, some cases, even in advanced stages, could have prolonged survival times.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

References

1. Delsol G, Campo E, Gascoyne, editors. In: WHO classification of tumours of haematopoietic and lymphoid tissue 4th Ed. IARC. 2008. p. 254–5.
2. Reichard KK, Mc Kenna RW, Kroft SH. ALK positive diffuse large B cell lymphoma: report of four cases and review of literature. *Mod Pathol*. 2007;20:310–9.



3. Randy D, Gascoyne RD, Lamant L, Martin-Subero J, Lestou VS, Harris NL, et al. ALK positive diffuse large B cell lymphoma is associated with Clathrin—ALK rearrangements: report of 6 cases. *Blood*. 2003;102:2568–73.
4. De Paepi P, Baens M, Van Krieken H, Verhasselt B, Stal M, Simons, et al. ALK activation by the CLTC-ALK fusion is a recurrent event in large B cell lymphoma. *Blood*. 2003;102:2638–41.
5. Delsol G, Lamant L, Mariane B, Pulford K, Dastungue N, et al. A new subtype of large B cell lymphoma expressing the ALK kinase and lacking 2, 5 translocation. *Blood*. 1997;89:1483–90.
6. Stachurski D, Miron PM, AL Homs S, Hutchinson L, Lee HN. Anaplastic lymphoma kinase-positive diffuse large B cell lymphoma with a complex karyotype and cryptic 3' ALK gene insertion to chromosome 4q22–24. *Hum Pathol*. 2007;38:940–5.
7. Beltran B, Castillo J, Salas R, Quinones P, Morales D, Hurtado F, et al. ALK positive diffuse large B cell lymphoma: report of four cases and review of the literature. *Journal of Haematology and Oncology*. 2009;2:11–4.
8. Wang WY, Ma ZG, Li GD, et al. Diffuse large B-cell lymphoma with expression of anaplastic lymphoma kinase protein: clinicopathologic and immunohistochemical study of 5 cases. *Zhonghua Bing Li Xue Za Zhi*. 2006;35(9):529–34.

Publish with Libertas Academica and every scientist working in your field can read your article

"I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely."

"The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I've never had such complete communication with a journal."

"LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought."

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

<http://www.la-press.com>