ALK Positive DLBCL - A Report of two cases and review of literature

ARUN PHILIP
Department of Medical Oncology, CANCER INSTITUTE (W I A)

Abstract:
Anaplastic Lymphoma Kinase (ALK) positive Diffuse large B cell lymphoma (ALK-DLBCL) is clinicopathologically unique, characterised by plasmablastic appearance, CD20 negativity and ALK positivity. It is a recently recognised subtype of lymphoma and has been included in the recent classification of lymphomas by WHO. Till date, close to 50 cases have been reported in literature. The disease has an aggressive course, and is often resistant to standard CHOP chemotherapy. We present two cases where Lymph node biopsy was suggestive of ALK - DLBCL. The first case is a 59 year old male with cervical adenopathy and cutaneous lesions. Though extranodal presentations are well known in this subtype of Non hodgkin’s Lymphoma, skin involvement has not been reported previously. The second case is a nodal presentation where the response to treatment was unsatisfactory and the patient had a disease relapse within a short duration. This highlights the relatively poor prognosis of this rare variant of DLBCL, in concordance with the existing literature.

A review of the existing literature pertaining to the ALK-DLBCL is presented here and possible suggestions to improve the clinical outcome in this poor prognostic subset of Non Hodgkin Lymphoma is put forward.

Keyword : Anaplastic Lymphoma Kinase (ALK), Diffuse large B cell lymphoma (DLBCL), Eosinophilic cytoplasm

Background:
Anaplastic Lymphoma Kinase (ALK) positive Diffuse large B cell lymphoma (ALK–DLBCL) is clinicopathologically unique, characterised by plasmablastic appearance, CD20 negativity and ALK positivity. It is a recently recognised subtype of lymphoma and has been included in the recent classification of lymphomas by WHO. Till date, close to 50 cases have been reported in literature. The disease has an aggressive course, and is often resistant to standard CHOP chemotherapy. We present two cases where Lymph node biopsy was suggestive of ALK - DLBCL. The first case is a 59 year old male with cervical adenopathy and cutaneous lesions. Though extranodal presentations are well known in this subtype of Non hodgkin’s
Lymphoma, skin involvement has not been reported previously.

**Introduction:**
Diffuse large B cell lymphoma is the most common subtype of Non Hodgkin's Lymphoma accounting for upto 40% of cases. ALK + Diffuse large B Cell Lymphoma was first described in 1997 by Delsol et al. This clinico pathologically unique entity shows plasmablastic differentiation and absent T & B cell markers making the diagnosis difficult. The prognosis is poor and the disease is often resistant to the standard CHOP chemotherapy. Role of Rituximab is unclear in view of a majority of cases being CD 20 negative.

**Case 1:**
A 59 year old gentleman, a diabetic and non smoker, presented to us with 2 months history of swelling in the right lower neck which was painless and rapidly growing in size. He never complained of cough, dysphagia, change in voice, fever or loss of appetite and weight. One week earlier, he had noticed extensive skin eruptions in the upper anterior chest wall. A right Level IV lymph node biopsy was performed elsewhere, which was reported as metastatic carcinoma. Physically, he was in good performance status. Neck examination revealed the scar in the right Level IV area with induration of skin around the same area. He had extensive erythematous, non pruritic, scaly eruptions in the posterior chest wall [Figure 1]. Other peripheral lymph nodes were not palpable. Hepatosplenomegaly was absent.

The lymph node biopsy slides were reviewed in our institute which demonstrated monomorphic proliferation of large lymphoid cells with eosinophilic cytoplasm, round-shaped central nucleus with high nuclear to cytoplasmic ratio, and prominent single nucleolus. Immunostaining with anti-ALK antibody showed finely granular cytoplasmic staining. A skin biopsy performed revealed no atypical cells. His CBC, renal and liver function parameters were within normal limits. There was no evidence of tumor lysis. LDH was 561. CT Chest & Abdomen revealed no other sites of disease. Bone marrow studies were normal.

The final diagnosis was Non Hodgkin's Lymphoma, ALK + Diffuse Large B cell Lymphoma, Stage iIAE, IPI 1/5. The patient was given 6 cycles of CHOP chemotherapy following which he had complete clinical response. He is on follow up and doing well at 28 months.

**Case 2:**
A 52 year old male was evaluated for Bilateral neck, Axillary and Inguinal swellings of 4 months duration. He did not have any B symptoms or any other swellings elsewhere. A Cervical Lymph node Biopsy was
performed which showed a morphological picture suggestive of DLBCL and Immunohistochemistry revealed CD45 positivity, CD79a positivity, Mild CD20 positivity and CD3 negativity. An ALK done thereafter was Positive. Staging investigations revealed no other sites of disease and the patient was diagnosed as a case of ALK-DLBCL, Stage IIIA. He was started on CHOP chemotherapy. A Partial Response was seen at the end of 4 cycles chemotherapy. He went on to receive 4 more cycles of CHOP chemotherapy. On follow up, he was detected to have relapse after a disease free Interval of 8 months. Relapse was confirmed by FNAC and he was stared on palliative oral chemotherapy.

Discussion:
The cases presented here are that of ALK positive Diffuse Large B Cell Lymphoma (ALK – DLBCL) diagnosed based on morphology and Immunohistochemistry. This entity was first described by Delsol et al in 1997. Pathological features include plasmablastic appearance with eccentric nuclei and single central nucleolus with abundant eosinophilic cytoplasm. Characteristically Immunohistochemical staining for CD 20, CD 30, CD 3 are negative and that for ALK, CD38 are positive. EMA and CK may be positive often leading to a misdiagnosis of a carcinoma. ALK positivity is usually cytoplasmic, though nuclear staining also has been described. CD 30 can be occasionally positive as in our case. This rare entity finds inclusion in the latest WHO classification of lymphomas. The differential diagnoses include lymphoblastic lymphoma, plasmablastic lymphoma or anaplastic variant of DLBCL. Extranodal presentations of ALK – DLBCL have been well described in literature. The case presented here had extensive skin lesions at presentation. However the biopsy was negative for the presence of atypical cells. The disappearance of the skin lesions after 2 cycles of chemotherapy may suggest involvement of the skin with ALK – DLBCL. Cytogenetic aberrations like CLATHRIN-ALK (2;17) and ALK–NPM t (2;5) rearrangements have been proposed as possible pathogenic mechanisms in this rare disease. Both were originally described for ALCL. The ALK – NPM protein results in ALK kinase activation, intracellular phosphorylation of residues and consequently lymphoma. Beltran et al summarised on the 50 cases reported to date on ALK – DLBCL. The important observations from this study include bimodal age of presentation, refractoriness to standard treatment with CHOP or paediatric NHL programmes and a call for newer strategies including consideration of anti myeloma treatment for improving the results. The Overall Survival quoted in this review is 56%. To summarise, ALK positivity is not exclusive to ALCL. ALK – DLBCL is a distinct type of Non Hodgkin’s Lymphoma with unique morphological and immunohistochemical features and refractory to standard therapy as seen with our second case. With the increasing awareness of such an entity, more and more cases are likely to be diagnosed in the future and more data may emerge on its clinicopathological behaviour that might help evolve better strategies to improve the overall outcome. Studies have shown that the adverse prognostic significance of bcl-2 and bcl-6 expression in DLBCL can be overcome by the addition of rituximab to CHOP chemotherapy. In similar lines, more data on this new entity will help formulate new therapeutic regimes to improve the results of treatment. An important development in this regard has been Crizotinib, an ALK fusion Tyrosine Kinase

An Initiative of The Tamil Nadu Dr. M.G.R. Medical University
University Journal of Medicine and Medical Sciences
Inhibitor that has been approved for treatment in ALK positive Non small cell Lung carcinoma in the second line which has also shown significant activity in ALK positive ALCL\(^8\). The clinical activity of this novel agent is yet to be tested in ALK-DLBCL and might be a possible step in the direction of a better clinical strategy in this poor subtype of DLBCL.

References


6. De Paepe et al, [ALK activation by the CLTC-ALK fusion is a recurrent event in large B-cell lymphoma]: Blood Oct 2003 _ Vol 102, N0 7
