EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 9
106-109
Year: 2020

ALK NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA WITH CUTANEOUS AND BONY PRESENTATION

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Article Received on 26/06/2020 **Article Revised on 15/07/2020** **Article Accepted on 05/08/2020**

ABSTRACT
Anaplastic large cell lymphoma (ALCL) consist of a proliferation of predominantly large lymphoid cells with strong expression of cytokine receptor CD30. Two major groups of ALCL have been described. First is a spectrum of CD30+ T cell lymphoproliferative disorder. Second is systemic nodal ALCL which is again subdivided into anaplastic lymphoma kinase (ALK) positive and ALK negative systemic ALCL. ALK expression is caused by chromosomal translocation most commonly t(2;5). We report the case of a 55 year old male presented with pain in right elbow. He had an enlarged left supraclavicular node. Xray showed a lytic lesion in supracondylar region of Right Humerus. Scanning revealed multiple enlarged nodes in mediastinum. Fine needle aspiration cytology from both the sites were showing scattered cells with marked nuclear atypia, multinucleation, prominent nucleoli and varying amounts of cytoplasm. Morphologically the cells, especially because they showed clustering in areas, were suggestive of Carcinoma cells, but multiple nodes being involved, suggested a Lymphoma. Biopsy was advised for a definite opinion. Biopsy from both the sites have showed diffuse sheets of pleomorphic cells, binucleate and multinucleate cells with moderate to abundant cytoplasm. Also noted cells with prominent eosinophilic nucleoli (RS like cells) and cells with reniform nucleus. Marker studies revealed that these cells are negative for Cytokeratin and LCA positive. Next line of markers included CD 30, CD 15, PAX-5 and EMA, of which PAX-5 was negative, thus ruling out Hodgkins Lymphoma. EMA was faint and focal positive. Epithelial like cells and RS like cells along with reinform nucleus were suggestive of Anaplastic large cells lymphoma(ALCL). EMA positivity was also supported this. ALK staining was done and found to be negative. Here the case was reported as ALK negative Anaplastic Large Cell Lymphoma. Unlike ALK positive Anaplastic Large Cell Lymphoma, this type is seen in fourth and sixth decades. Both nodal and extranodal sites like bone, soft tissue and skin are affected. Cells may show cohesive pattern mimicking carcinoma. Prognosis is poorer than ALCL-ALK positive cases.

KEYWORDS: ALK negative, anaplastic large cell lymphoma, immunohistochemistry, PAX 5 negativity, bony and cutaneous lesions.[3]

INTRODUCTION
Differentiation of High grade Lymphoma and poorly differentiated carcinoma is clinically very difficult. High grade Lymphoma mostly show cells with appreciable amount of cytoplasm and large and vesicular nucleus with prominent nucleoli. Generally cohesive clusters, abundant cytoplasm and marked pleomorphism are suggestive of carcinoma. Diffuse sheets of cells with prominent nucleoli and monotonous population are in favour of lymphoma.

However, poorly differentiated carcinoma show dyscohesive clusters or diffuse sheets of cells. Cell morphology also can vary from cells with minimal to abundant cytoplasm. On the other hand, high grade lymphoma like ALCL show cells with abundant cytoplasm and marked pleomorphism making the differentiation difficult. This was overcome with the systematic use of IHC markers. Hence it has a great role in distinguishing Poorly differentiated carcinoma and high-grade lymphoma.

MATERIALS AND METHODS
1. Two wet fixed Papanicolaou and a dry fixed Giemsa stained slides.
2. Two submitted slides (USG guided)- Papanicolaou and Giemsa stained.
3. Hematoxylin and Eosin stained slides.

4. Immunohistochemical markers.
5. 95% Ethanol.
6. 40% Formalin.

Fine needle aspiration cytology study was done on the Left supraclavicular enlarged lymphnode after physical examination and under sterile precautions. Two slides were put in 95% Ethanol soon after spreading the aspirate on to the slide surface and the spreader slide was kept dry. All the slides were sent for processing and staining. We used two stains, Papanicolaou for two wet fixed slides and Giemsa for dry fixed slide.

Also received two submitted slides by Ultrasound guided Fine Needle Aspiration Cytology study from lytic lesions over Right supracondylar region. Both the slides were stained with Papanicolaou stain and observed under microscope.

Biopsy study on Left enlarged supraclavicular node using Hematoxylin and Eosin stains revealed atypical cells and under the light of which further detailed studies using Immunohistochemical markers were done, as follows.

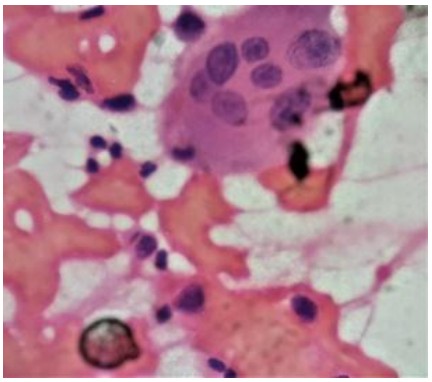
- First Panel markers: Cytokeratin(CK) and Leucocyte common antigen(LCA).
- Second Panel markers: PAX5, CD30, CD 15 and EMA.
- Third Panel marker: Anaplastic Lymphoma Kinase(ALK).

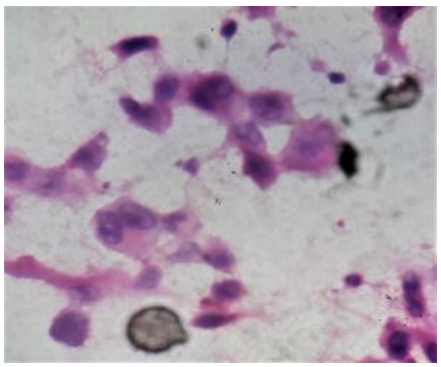
RESULT

A 55 year old male presented with left supraclavicular lymph node enlargement for a duration of 2 years and a swelling over right supracondylar region for 1 year. He was referred to cytology lab to do FNAC from both the lesions. On examination of supraclavicular node, findings noted are -1.5x1.5x1.0 cm in size, firm to hard in consistency, immobile and normal overlying skin. FNAC study on the lesion showed diffusely scattered cells with abundant cytoplasm, pleomorphic vesicular nucleus with marked atypia, binucleate and multinucleate forms with prominent nucleoli. Also noted RS like cells with horseshoe shaped nucleus and many Mitotic figures. Some cells are arranged in sheets. On further examination of medical reports X Ray shown lytic lesions over right supracondylar region which is corresponding to cutaneous swelling. MRI thorax showed multiple mediastinal lymph nodes. The lytic lesion in supracondylar region was also aspirated and slides were submitted. Those smear was also shown similar cells as in lymph node cytology. The arrangement of cells in sheets and morphology of cells was suggestive of an Epithelioid neoplasm. Involvement of bone was favouring Carcinoma. But multiple lymph node involvement suggested a Lympho proliferative neoplasm. With these findings diagnosis given was either secondary from poorly differentiated carcinoma or high grade Non Hodgkin's lymphoma.

Hence, histopathology evaluation was suggested. Biopsy from supracondylar region show pleomorphic anaplastic large cells few showing horseshoe shaped nucleus and voluminous cytoplasm (RS like cells), prominent nucleoli areas of necrosis and haemorrhage with 2 to 3 mitotic figures per high power field. Two weeks later biopsy from supraclavicular lymph node was taken which also showed similar morphology.

On view of these findings immunohistochemical studies were done. The markers used were: LCA, CK, CD20, CD3. The second line panel markers are PAX5 and CD15. With these markers the given differential diagnosis was either Hodgkin's lymphoma or anaplastic large cell lymphoma. Later EMA and ALK markers were also done.



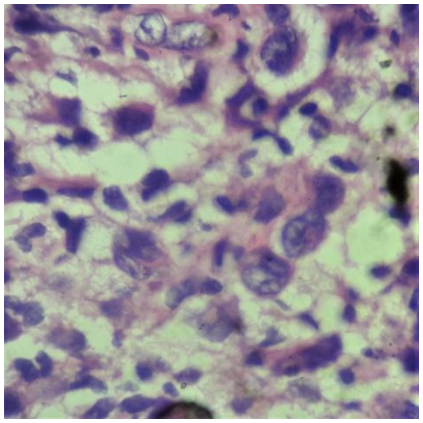
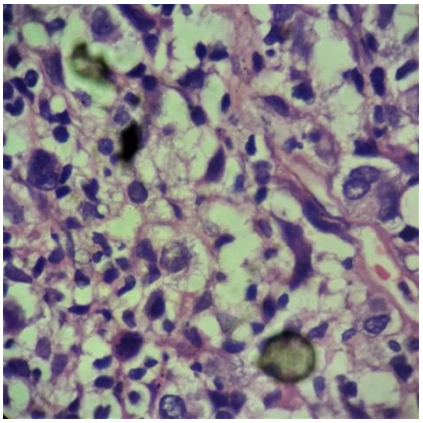


REPORT

Diffusely scattered cells with marked nuclear atypia. Binucleate/multinucleate forms seen. RS like cells also noted.

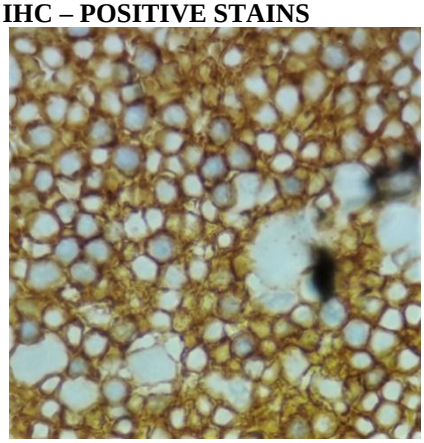
DIAGNOSIS

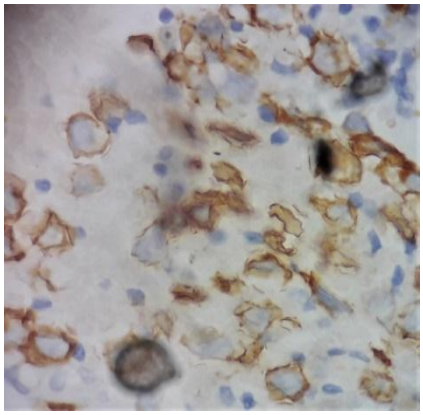
Poorly differentiated carcinoma / High grade NHL

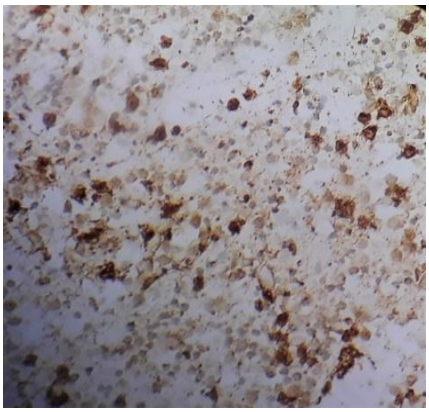



Marked pleomorphism with prominent nucleoli.
Horse shoe shaped nuclei and RS like cells.

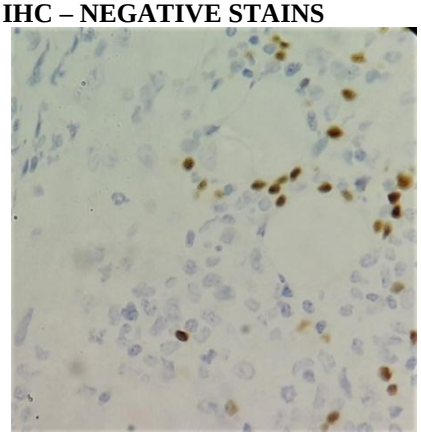
IHC – POSITIVE STAINS

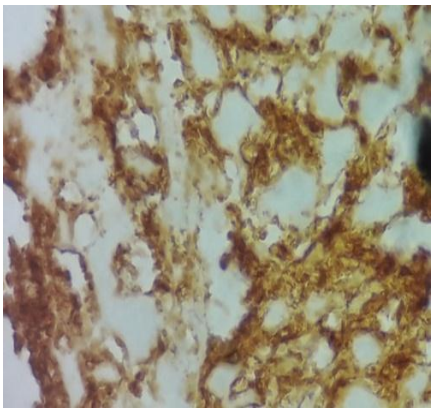

LCA

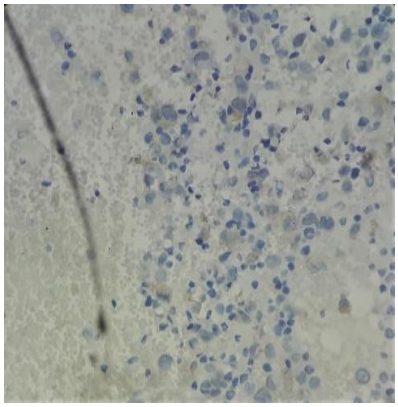

EMA


CD 30

IHC – NEGATIVE STAINS


PAX 5


CD 15


ALK

DISCUSSION

Primary systemic ALCL is the most frequent subtype of ALCL, accounting for 2-8% of Non Hodgkin's lymphomas in adults. ALCL was first identified by Stein et al as a new lymphoma category and defined on the basis of anaplastic appearance of the tumour cells, their propensity to grow cohesively and to invade node sinuses and the consistent expression of the cytokine receptor CD30 on all or nearly all neoplastic cells.[1] The monomorphic variant is the most common type of ALCL. Masson et al have described it as being associated with nonrandom chromosomal translocation t(2;5)(p23;q35).[2] Morris et al cloned the genes involved in the translocation, identifying the gene on chromosome 2 as a newly described tyrosine kinase named the anaplastic large cell lymphoma kinase (ALK), which fused with nucleophosmin (NPM) gene chromosome.[4] ALK protein has recently been used to detect full length nucleophosmin-ALK fusion protein in tumour biopsies. Expression of ALK protein is demonstrated in approximately 60% of ALCL and it is present most frequently in the 1st 3 decades of life. In recent years,

there has been growing interest in identifying specific molecular features that in addition to histologic type and clinical status may help to define the prognosis in patients with aggressive lymphomas. Systemic ALCL expressing the NPM-ALK protein has a better prognosis showing an 80% 5 year survival rate compared with a rate of 30% for other ALK negative cases. An increase in immunoglobulin levels has been found in this type of neoplasm, as occurs in B cell lymphomas.[5]

CD3 pan T cell marker, most widely used, is negative in greater than 50% of cases, and is more pronounced in nodal ALCL, although, in our patient, it was negative.[6] These tumors are not associated with EBV, and HTLV-1 has been detected in 39.5% of cases of CD30+ ALCL in an HTLV-1 endemic area. There is a marked male predominance, upto 6:1 in some series. Smoking has not been associated with T-cell lymphoma, but drinking significantly increases the risk of the disease. Several Ophthalmic abnormalities have been described in patients with cutaneous T-cell lymphoma. In our patient, ophthalmic examination was normal. Patient with multifocal skin lesions should be treated with chemotherapy, although a waiting period for possible spontaneous regression may be allowed. In patients with full blown disease or developing regional lymphnode involvement, multiagent chemotherapy is still considered to be the safest option. Skin relapses after chemotherapy are common, but they are not associated with an aggressive clinical behaviour and therefore do not require an aggressive approach.[9] The role of the International Prognostic Index 19 for predicting the outcome of CD30+ ALCL is a matter of debate. It was developed for aggressive NHL, and comprises five clinical parameters, including age, stage, number of extranodal sites, LDH level and performance status. Our patient had a poor prognosis; but the clinical evolution has been good.[8]

CONCLUSION

ALK negative anaplastic large cell lymphoma is a T cell lymphoma with strong CD30 expression which invades both nodal and extranodal sites. It has a poorer prognosis than ALK(+)ALCL but better prognosis than cutaneous T cell lymphoma, which is the closest D/d. Recent studies have shown that DUSP22 rearrangements occur in ALK(-)ALCL with favorable prognosis. Responsive to doxorubin containing chemotherapy (CHOP REGIMEN). CD30 is a newer therapeutic target and brentuximab vedotin (anti CD30) has been used for relapsed/refractory systemic ALCL.[7][10]

ACKNOWLEDGEMENT

I wish to record my deep sense of gratitude and profound thanks to Dr Seena A R, Associate Professor and Dr LailaRani vijayaraghavan, Professor, in Pathology, Government Medical college, Thiruvananthapuram for her keen interest and inspiring guidance, constant encouragement with my work during all stages, to bring this paper into fruition. I also wish to thank my family and friends for the immense support.

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