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CYTOMORPHOLOGY OF PAEDIATRIC ANAPLASTIC LARGE CELL LYMPHOMA AT RARE EXTRANODAL SITES – CASE SERIES

Pathology

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ABSTRACT

Objective: Anaplastic large cell lymphoma (ALCL) is a relatively rare form of non-Hodgkin lymphoma in children constituting 10–15% of this entity. The aim of this study was to describe the role of Fine needle aspiration cytology (FNA) in diagnosing Alk positive ALCL at rare sites by combining cell block and ancillary tests.

Materials and Methods: Five paediatric cases of Alk positive ALCL were retrieved from the cytology register. All were boys, youngest aged 11months and oldest being 13yrs. They presented at rare sites involving oro-nasopharyngeal, mediastinal, thigh, arm, supraorbital & scalp. FNA and cell block was done & one case of mediastinal lesion FNA was performed under ultrasound guidance. The clinical and cytomorphological features including ancillary tests were reviewed.

Results: Cytomorphology of all the five cases revealed high grade lymphoma with large lymphoid cells with abundant cytoplasm, horseshoe shaped nuclei and wreath-like multinucleated giant cells.

Conclusion: ALCL is very aggressive high grade T cell lymphoma. It can occur at rare sites as highlighted in our cases. ALCL can be accurately diagnosed by FNA cytomorphology, along with ancillary tests on cell block. This study emphasizes the need for clinicians and pathologists to maintain a high index of suspicion for ALCL when patients present at such rare sites.

KEYWORDS

Anaplastic Large Cell Lymphoma, Immunohistochemistry, Extranodal.

Background:

Alk positive Anaplastic large cell lymphoma (ALCL), is a CD30+ T-cell lymphoma . ALCL was first described by Stein et al. in 1985 (2) . It accounts for 10–15% of all Paediatric NHL (1). Alk + ALCL present at an advanced stage of disease. Common translocation–t (2;5) (p23;q35). 1/3rd children treated with modern multi-agent chemotherapy regimens - disease recurrence (3).1/2 of those will ultimately die of their disease. The cells of Alk positive ALCL show varied cell morphology with large neoplastic cells with abundant cytoplasm and pleomorphic often eccentric horseshoe- or kidney-shaped nuclei (Hallmark cells), doughnut cells, Para nuclear eosinophilic Hof(1), this makes the diagnosis challenging on fine needle aspiration cytology (FNAC). NHL usually occurs in lymph nodes, but ALCL frequently involve various extranodal sites such as the skin, bone, orbit, gastrointestinal, lung, and central nervous system. Primary involvement of extranodal sites by ALCL is less frequent than the primary nodal counterpart. To our knowledge, only a few cases were reported previously, which were mainly in adults. The current study describes 5cases of Primary extranodal Alk positive ALCL in children at rare sites with detailed clinical & cytopathologic examinations. .Here we highlight the fact that fine needle aspiration cytology when combined with immunohistochemical study on cell block forms an efficient diagnostic tool.

Materials & Methods: Five paediatric cases of Alk+ ALCL that presented at rare extranodal sites were retrieved from the archives between Jan2013 and July2018. Clinical and laboratory information were obtained from the medical records department for all five cases. All were boys, youngest aged 11months and oldest being 13yrs. They presented at rare sites involving oro-nasopharyngeal, mediastinal, thigh, arm, scalp & supraorbital. Fine needle aspiration procedure was performed after taking patient consent .Four cases had routine & one had Ultrasonography guided FNA. All the PAP, MGG stained slides were reviewed, IHC that were performed on Cell Block material was also reviewed. Cell block was prepared by Formalin fixed, Agar method .The list of the IHC markers along with the details of manufacturer and dilutions are given below (Table1).Conventional cytogenetics & histopathological review were also done wherever available. Further molecular analysis could not be performed due to financial constraint.

Table 1: List of IHC Antibodies .

Antibody	Clone	Dilution	Manufacturer
CK	C11	1:20	Biogenex
LCA	LCA88	1:400	-
CD3	PS1	1:100	-
CD20	L26	1:100	-
ALK	Sp8	1:30	-
EMA	E29	1:100	-
MyoD1	LO26	1:100	-
Desmin	33	1:100	-
CD4	4B12	1:60	-
CD5	4C7	1:60	-
Ki67	BGX-297	1:100	-
CD34	QBEND34	1:40	-
CD99	Ho36.1.1	1:40	BioSB
CD15	467	1:250	Biogenex
Tdt	NPT26	1:100	BioSB
CD30	HRS4	1:10	Biogenex

Results: Case 1: An 11 month old infant presented to the department of Pediatric oncology with snoring and mouth breathing since 1month

.On admission clinically the patient was in bad condition. His medical and family history was unremarkable. On physical examination, there was no peripheral lymphadenopathy. Head & neck examination revealed a soft bulge in the oropharynx, measuring about 30x20 mms. Mucosa over the bulge appeared normal. Spleen was palpable around 2cms from coastal margin .All other systems were normal. Peripheral smear revealed normocytic normochromic with mild thrombocytopenia. Bone marrow aspiration showed normal Trilineage haematopoiesis. Biochemical parameters were all normal except for mild increase in LDH (392 U/m**).** Renal function test & liver function tests were normal .Serological tests for HIV, HBSAg, HCV were nonreactive. CECT head & neck showed a homogenous soft tissue mass measuring 50x53x36 mms epic entered in naso-pharynx and oropharynx (fig 1 a). Extension to the right spheno-palatine and pterigo-maxillary fossa with occlusion of naso-pharyngeal and oro-pharyngeal air way was noted. PET scan ratified same & revealed the extension of the same mass of 34x39x38mms into oropharyngeal region. There was mediastinal lymphadenopathy measuring 1.7x2.5cm & Splenomegaly was also noted. A radiological differential diagnosis of Angiofibroma &Lymphoma was offered .Fine needle aspiration of the Oropharyngeal lesion was done with the assistance of ENT surgeon in the department of cytology using 23 gauge needle attached to 10ml syringe. Aspirate was also sent for the cytogenetic study. FNAC of the mass showed predominance of large pleomorphic, atypical cells with large nuclei, few having horse shoe shaped nuclei. Few multinucleate cells were also seen. Occasional cells showed eosinophilic region near the nucleus. Few cells had vacuolated cytoplasm. Many atypical mitotic figures were seen. Smears were interpreted as poorly differentiated malignant tumor, possibilities considered are, malignant lymphoma– ALCL&Rhabdomyosarcoma (fig1c).

Immunophenotyping of the FNA material revealed the gated population of cells to be positive for cCD3 and CD30 (fig1b). Correlating FNA morphology and IPT findings, features suggestive of CD30 Positive T-Cell Lymphoma was offered. Cell block showed few hallmark cells along with these pleomorphic large cells (fig1d). Immunohistochemistry on cell block revealed the neoplastic cells to express LCA (focally), CD3, CD30, ALK, MIC2 and n*egative* for CD20, Desmin (fig 1). Correlating clinical, radiologial, pathological findings a diagnosis of Alk positive Anaplastic Large cell lymphoma was made. It was Stage III disease and patient was started on chemotherapy after tracheostomy. But the child succumbed to the disease after the first cycle of Chemotherapy due to internal bleeding.

Case 2 : 5 years 8 months old boy presented to department of pediatric oncology with chief complaints of engorgement of veins in the neck since 1 ½ years , fever & cough since 2 weeks .Increasing prominence of veins was noted during cry in the initial few months followed by permanently engorged veins. Fever was moderate grade & not associated with chills/ rigors. Cough was non paroxysmal, aggravated by lying down, not associated with sputum. There was no history of voice change, dysphagia. No history of pallor/ bleeding tendencies / ulcerative lesions .No history of loss of weight or appetite. His family history was unremarkable. General physical examination showed clubbing, facial puffiness, engorgement of veins in the neck and chest wall. On examination there was no pallor/cyanosis/peripheral lymphadenopathy. Respiratory system revealed mild decrease in intensity of breath sounds on right side with fullness of the chest wall .No added sounds/evidence of effusion .Cardiovascular system was normal .Per abdomen did not show any organomegaly .CNS examination was normal . With clinical impression of lymphoma/germ cell tumor/neuroblastoma the patient was investigated. Haemogram, Viral markers were normal .Biochemistry showed mildly increased LDH (253 U/m). Chest X ray showed mediastinal widening with large radio dense opacity obscuring ascending aorta and arch of aorta- possibly anterior mediastinal mass, no erosion of sternum or vertebrae was seen .Ultrasound abdomen was normal. ECG was normal & Echocardiogram showed mild pericardial effusion. CECT thorax revealed a hypodense lesion in the anterior mediastinum with peripheral mild post contrast enhancement and central nonenhancing areas, abutting sternum anterioriorly with no erosion & compressing trachea posteriorly (fig2a). Radiologically a possibility of Lymphoma /Germ cell tumor was suggested. Bone marrow aspirate was normal. CSF did not show any infiltration. Patient underwent ultrasound guided fine needle aspiration of the anterior mediastinal mass under aseptic precaution. Smears showed occasional crushed tight cell clusters with a few lymphoid cells. Occasional large cells with poor cell morphology were also seen (fig2b). Cell block showed sheets of small to medium sized cells with few histiocytes and occasional large cells with eccentric nuclei especially around blood vessels (fig2c). Smear for ZN Staining was negative for acid fast bacilli .IHC on cell block was done and reviewed. The large cells were positive for LCA, CD30 (fig2d), ALK (fig2e) .CD4, CD5 was positive only in scattered cells. Ki67, the proliferative index was high around 90% .CD34 staining highlighted the blood vessels. They were negative for CK, Desmin, MyoD1, MIC2, CD3, CD20, and CD15, Tdt. Correlating clinical and radiological findings a diagnosis of Alk positive ALCL of the mediastinum, Stage III was given. Cytogenetics did not yield any metaphase. Patient was started on chemotherapy .However after the four cycles of chemotherapy the PET CT showed metabolically active supra and infradiaphramatic lymphadenopathy, active lesions in lung, liver, kidney, paranasal sinuses, left Sartorius muscle. FNA of the nodular lesion over the scalp showed similar cell morphology suggestive of relapse. Patient succumbed due to respiratory failure by mediastinal compression.

Case 3: 13 year old boy was referred from NIMHANS with history of swelling over scalp since 3 months and paraplegia . On examination swelling over the scalp in the left frontal region measured 4x3 cms. The biochemical, haematological and serological tests were within normal limits . Chest x ray, abdominal ultrasonography and echocardiogram was normal . Cranial CT done showed lytic erosions in the left frontal bone with extradural component at left frontotemporal region measuring 4.3x.5 cms with overlying enhancing scalp swelling.

Radiological differential of LCH/Tuberculosis was offered. Bone scan showed increased uptake in calveria, multiple vertebrae D8-L1 .Bone scan showed features suggestive of skeletal metastasis. Bone marrow aspiration revealed reactive hyperplasia. Cytogenetics on the bone marrow was normal karyotype. FNA of the scalp swelling revealed malignant cells & possibilities considered were ALCL/LCH/?RMS (fig3a).IHC on cell block (fig3b) showed the tumor cells to be positive for Alk(fig3d),CD30(fig3c),EMA,CD3 and were negative for CD138,CD1a,CD 20,CD99 ,Myod1 ,S100 .Final diagnosis of Alk positive ALCL Stage III was offered. Patient was started on chemotherapy and radiotherapy. Patient completed one cycle of chemotherapy. There was increased uptake in parietal bone and later patient died.

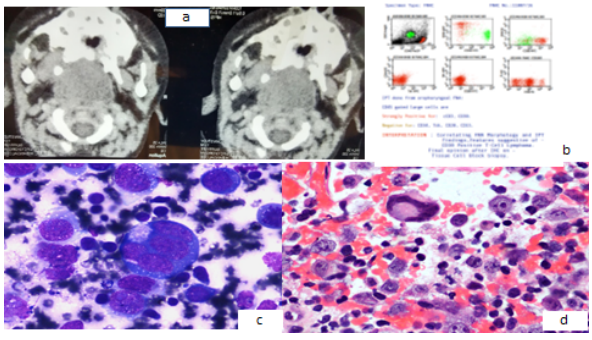
Case 4: 10year old boy presented with swelling over dorsum of left wrist associated with pain and fever since 10days .There was also history of sequential swelling involving left thigh, right thigh, right leg, anterior chest, lower back and left arm . Patient was referred to our institute from elsewhere with biopsy diagnosis of Rhabdomyosarcoma. On examination there was swelling as described and ranging in size from 1x1cms to 3x4 cms. Biochemical parameters were within normal range except high LDH (770U/L) .CBC showed low total leukocyte count of 2900/cmm. Chest x ray was normal. X ray AP of the thigh showed soft tissue opacity in upper third of left thigh and diagnosis of soft tissue sarcoma was rendered radiologically. Ultrasonography abdomen revealed well defined hypoechoic lesion along liver surface msg 1.6x2.6cms. Similar lesions were seen in peripancreatic region, periumbilical and lower pole of kidney. CECT thigh showed multiple predominantely intramuscular neoplastic masses and nodules in all compartments of bilateral thigh. Bone scan revealed multiple skeletal secondaries. FNA was performed from bilateral thigh swelling and showed Poorly differentiated malignant tumor , possibility of ALCL was given (fig4a) . Review of earlier biopsy showed a neoplasm composed of round to oval cells displaying eccentric nucleus and eosinophilic cytoplasm (fig 4b, biopsy). Cells were arranged in solid sheets and were seen infiltrating the skeletal muscle fibres .Mitosis was around 8-10/10hpf .IHC was performed. The tumor cells were positive for LCA, CD30 (fig4d), EMA, CD20, ALK (fig4c) and they were negative for CK, desmin, myogenin. Cytogenetics on FNA material showed 44, XY, t (2, 5) (p23; q35). A diagnosis of Alk positive ALCL Stage IV was rendered. Patient was started on chemotherapy however he died due to sepsis and respiratory distress.

Case 5: 11 yr old boy came with history of swelling over the left medial supraorbital since 20 days. On examination swelling was soft to firm, nontender, 2x3 cms. The biochemical, haematological and serological tests were within normal limits. Chest x-ray, abdominal ultrasonography and echocardiogram were normal. CT scan of the head showed soft tissue density mass lesion measuring 10.6x19x26 mm in the supraorbital region extending inferiorly up to inner canthus of the left eye .Underlying bone was normal .Bone scan was normal . Cytogenetics

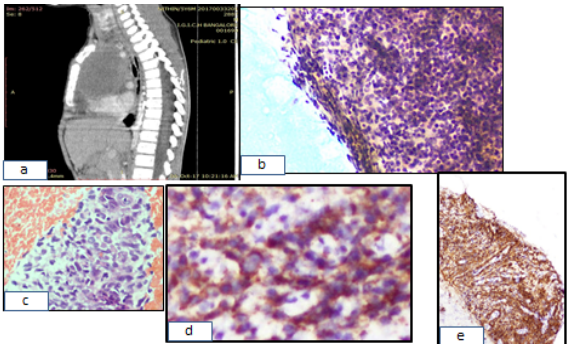
on the bone marrow was normal karyotype. FNA of the swelling revealed histiocytic clusters, scattered large cells with basophilic cytoplasm, plasmacytoid cells, binucleate cells, large mononuclear cells and numerous atypical mitosis. A possibility of ALCL/LCH was given. Patient had biopsy elsewhere and review of earlier biopsy showed diffuse infiltration of histiocytes,occasional mononuclear large cells,mature lymphocytes and occasional plasma cells .

IHC revealed the large neoplastic cells positive for LCA,CD30,EMA ,CD4,CD5, ALK and they were negative for Cd1a, Cd68, CD3,CD20,CD138,PAX5. CD68 highlighted histiocytes .Ki67 was 65%. Final diagnosis of Alk positive ALCL Stage I was offered. Patient is started on chemotherapy and radiotherapy. He is on follow up.

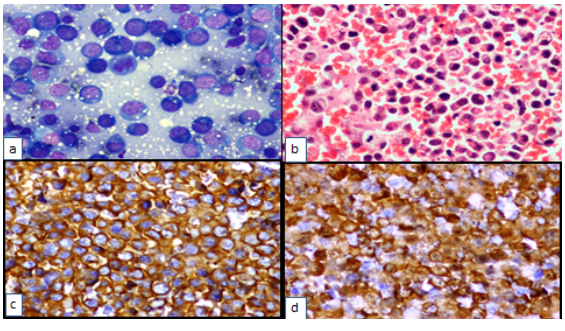
Case 1: Fig 1(a-d)



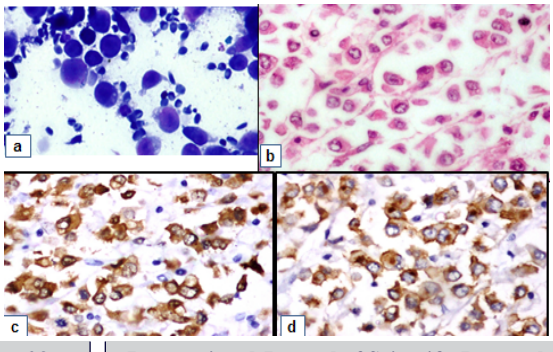
Case 2: Fig 2(a-e)



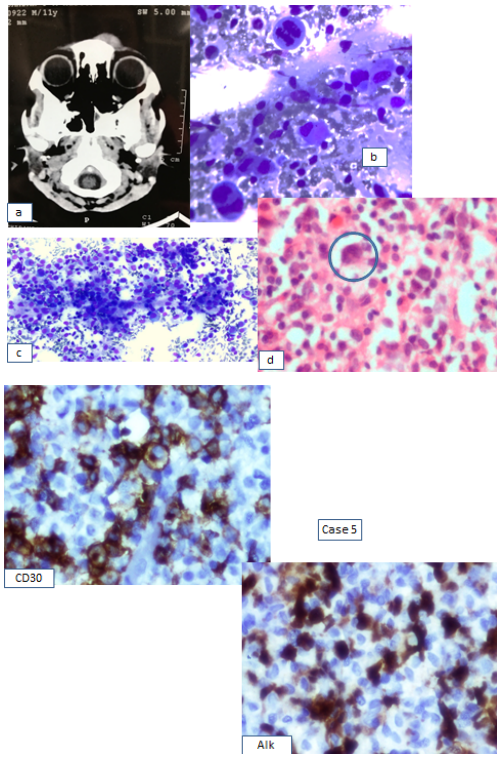
Case 3: Fig 3



Case 4: Fig 4



Case 5: Fig 5



Cytopathology of the five cases: Cytomorphology of the three cases revealed high grade malignant tumour with large atypical cells with abundant cytoplasm, horseshoe shaped nuclei and wreath-like multinucleated giant cells. One case of mediastinal lesion showed hypocellular areas with necrosis and was confirmed by immunohi stochemistry. Last case was a lymphohistiocytic variant of ALCL that had numerous histiocytes masking the large neoplastic cells .All cases were ALK positive both cytoplasmic and nuclear, except case 4th that showed cytoplasmic staining (Table4). Based on the cytomorphology and IHC on cell block study the patients were started on chemotherapy. However four patients died during the course of chemotherapy and case of lymphohistiocytic ALCL is on chemotherapy. (Table 2& 3).

Table 2:

Results : Summary of clinical features of four cases of ALCL

Case	Age	Sex	Clinical presentation	Primary site	BMA involvement
1	11mnth	M	Snoring & mouth breathing	Oropharynx	No
2	5yr 8mnt	M	Fever,cough,engorged neck veins	Mediastinum	No
3	13yr	M	Scalp swelling, paraplegia	Bone	No
4	10yr	M	Fever, swelling left wrist	Intramuscular	No
5	11yr	M	Swelling left supraorbital	Soft tissue	No

Table 3:

Case	stage	Therapy	Survival	Outcome
1	III	Tracheostomy , 1 cycle CT	15days	Died due to internal bleeding
2	III	4 cycles CT, widespread involvement (PET) ,Scalp-relapse	6mnths	Died – Respiratory failure by mediastinal compression
3	III	4 cycles CT, RT, increase uptake parietal bone	6mnths	died
4	IV	CT	15days	Died due to sepsis, respiratory distress
5	I	CT	On follow up	

Table 4:

Results : Immunohistochemical characteristics of five cases

Case	CD45	CD 3	CD20	CD30	ALK	EMA	CD15	MIC2	Desmin
1	+focal	+	_	+	+ N,C	+	_	+	_
2	+	_	_	+	+ N,C	+	_	_	_
3	+	_	_	+	+ N,C	+	_	_	_
4	+	_	_	+	+ C	+	_	_	_
5	+	_	_	+	+N,C	+	-	Not done	Not done

Discussion: Anaplastic large cell lymphoma (ALCL) is a relatively rare form of non-Hodgkin lymphoma (NHL) in children constituting 10–15% of this entity (1). The latest World Health Organization (WHO) Classification recognizes following distinct subtypes: primary systemic anaplastic lymphoma kinase positive (ALK+ ALCL) been our case, primary systemic anaplastic lymphoma kinase negative (ALK- ALCL), primary cutaneous types (pC-ALCL), Breast implant-associated ALCL (BI-ALCL) (3). Since ALCL was first recognized by Stein et al. in 1985, significant achievements have been made in the study on the pathology of this disease over the years.

The role of FNAC in the diagnosis of ALCL has not been well recognized. The largest series from India were from Das et al (7 cases) (18) and Prashanth et al (20 cases) (19). There are only few case reports from India highlighting the occurrence of ALCL at rare extranodal sites. Our case series highlights the rare extranodal involvement of ALCL with soft tissue infiltration & role of FNA in diagnosing ALCL in Paediatric patients. It is exceedingly rare in infants, with a median age at diagnosis of 12 years. One of our cases was 11month old and highlights the development of ALCL-ALK (+) in infants that is very rare, with only very few case reports in the literature (10, 11, 12, 13, and 17).(Table 5)

A study by Rapkiewicz et al. (7) also dealt with the cytomorphology of ALCL. They studied a total of 37 cases in which FNAC smears, or liquid cytology preparations and/or histology slides were available. In this series, they were able to make a diagnosis of ALCL in 13 cases primarily on FNAC smears (including one primary diagnosis and 12 other cases previously diagnosed as ALCL).

In the present study, cytomorphology of all the four cases revealed high grade malignant tumour with large atypical cells with abundant cytoplasm, horseshoe shaped nuclei and wreath-like multinucleated giant cells. One case of mediastinal lesion was challenging due to the presence of small to medium sized cells mimicking like reactive process with necrosis .Tumour cells were highlighted by CD30 & Alk immunostains and were clustered around blood vessels .Three cases had cell block and immunohistochemistry & final diagnosis was rendered on cell block . Two cases however had prior biopsy and same was confirmed on IHC.

Table 5:

Serial no	Case report/series	Median Age	No of patients
1	Ben Barak et al	2 months	1
2	Sebire etal	5mnths	1
3	Rubie H etal	11mnths	1
4	Greer etal	4mnths	1
5	Tariq etal	<1yr	2
6	Ferster etal	7mnths	1
7	Khor etal	<1yr	1
8	Andrea etal	6 mnths	1
9	Our case	11mnths	1

The diagnosis of ALCL by FNAC is not only difficult but challenging if it occurs at an unusual sites such as the scalp, oropharyngeal region, mediastinum,supraorbital,extremities although the hallmark cell is a clue for the diagnosis. These are characteristically described as CD30-positive anaplastic pleomorphic cells with abundant amphophilic cytoplasm, reniform nuclei and Para nuclear eosinophilic Hof. These hallmark cells are known to show varied cytomorphology and cohesion with clustering around blood vessels, thus creating diagnostic dilemmas. Our case of mediastinal ALCL showed tumour cells around blood vessels.

The current study highlights the need for cytopathologists to maximize the accuracy, efficiency, and effectiveness of FNA by allocating aspiration material to several modalities. This may include preparing a cell block for immunocytochemistry and polymerase chain reaction, and fresh material for cytogenetics and flow cytometry. ALCL can be accurately diagnosed by FNAC by combining morphology, IHC on cell block , Immunophenotyping , under expertise hands . Case 1 had flow cytometry on FNAC material and this facilitated to work on cell block,IHC for final diagnosis .Such lesions due to their rarity and complexity remain diagnostic challenges that necessitate a high degree of clinical suspicion for accurate identification to guide early appropriate treatment. This study also highlights the importance of obtaining adequate material, keeping a wide differential diagnosis, and utilizing both immunohistochemistry and molecular techniques when one encounters an anaplastic neoplasm and this cannot be underestimated. CD30 status is no longer sufficient for a diagnosis of ALCL because the prognostic implications of ALK are significant. Primary oropharyngeal Alk Positive ALCL is rare in children. A study done by Anjali et el (20) in 2016 , showed only two pediatric cases in the pubmed literature .Primary soft tissue Alk positive ALCL though rare have been reported in children Yang et al in 2015 (21) . Lymphohistiocytic variant accounts for 10% of cases in WHO & carries good prognosis as compared to other variants .Our case is on chemotherapy and Stage I .Primary Bone Alk positive ALCL is also very rare in children. Study done by A.Ng et al in 2007 (5) looked at the Cases of ALCL with bone disease from the NHL clinical trial forms and database at the United Kingdom Childhood Cancer Study Group (UKCCSG) Data Centre in Leicester.There were only three primary Alk positive ALCL in children .

Conclusion: ALCL is very aggressive high grade T cell lymphoma. It can occur at rare sites as highlighted in our cases. ALCL can be accurately diagnosed by FNA cytomorphology, along with ancillary tests on cell block, under expertise hands. This avoids the biopsy especially in paediatric patients and decreases the turn over time. This study emphasizes the need for clinicians and pathologists to maintain a high index of suspicion for ALCL when patients present at such rare sites.

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