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Anaplastic Kinase-Positive Large T-cell Lymphoma Simultaneous with Tuberculosis in a Child: a Case Report

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Abstract

Anaplastic lymphoma kinase-positive (ALK+) large T-cell lymphoma (ALCL) is a rare type of lymphoma and it involves lymph nodes, but in some rare situations, it involves lungs, firstly. There are very rare cases in the world that have this type of disorder complicated with tuberculosis (TB). In this report, we present a boy who was referred to our hospital with TB and ALK+ALCL.

Key Words: Anaplastic, Lymphoma, Tuberculosis.

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1- INTRODUCTION

Anaplastic large cell lymphoma (ALCL) with expression of ALK (ALK+ ALCL) is an uncommon subtype of peripheral T-cell lymphoma (PTCL) (1). About 10–15% of non-Hodgkin lymphomas (NHL) in pediatrics are ALK+ ALCL (2). Lung involvement occurs in less than 15% of pediatrics with ALK+ ALCL (3). In CT scanning, Lymphomatous infiltration, interlobular septal thickening, and granulomatous consolidation can be seen, and this may be similar to pneumonia or military tuberculosis (4). Patients with a history of tuberculosis (TB) have a considerably higher risk of non-Hodgkin lymphoma (NHL) (odds ratio=1.8). Extrapulmonary tuberculosis and lymphomas in the same organ are uncommon (5-6). In this case, we report a complicated boy with ALK+LBCL and TB.

2- CASE PRESENTATION

The patient was a 13-year-old boy, the second child in the family and was the result of a consanguineous marriage who had been hospitalized due to lung disorders to the Children's Medical Center (Tehran, Iran) with fever and respiratory distress. He had a complete vaccination history and no underlying disorder.

Ten days ago, he was admitted to another center with fever, respiratory distress, and right unilateral upper and middle lobe pneumonia. In that center, several workups were performed for him such as bronchoscopy for foreign body ruling out; and the possibility of COVID-19 was also evaluated, but there was no diagnosis for him and antibiotics (Ceftazidime + Vancomycin) were administered but there was no response to these antibiotics. Then, he was referred to our center (Children's Medical Center) with severe non-productive cough, anorexia, weight loss of about 2 kilograms during 3 months ago. In physical examination, there was respiratory distress with decreased pulmonary sounds in the right lung. All signs including meningitis signs, hepatosplenomegaly, lymphadenopathy, and other examinations were negative. His vital signs at admission time were (RR: 23, HR: 120, BP: 105/80, T: 38.5, O2 SAT: 93%). Chest X-ray was taken and it was compatible with TB in its report (**Fig. 1**).

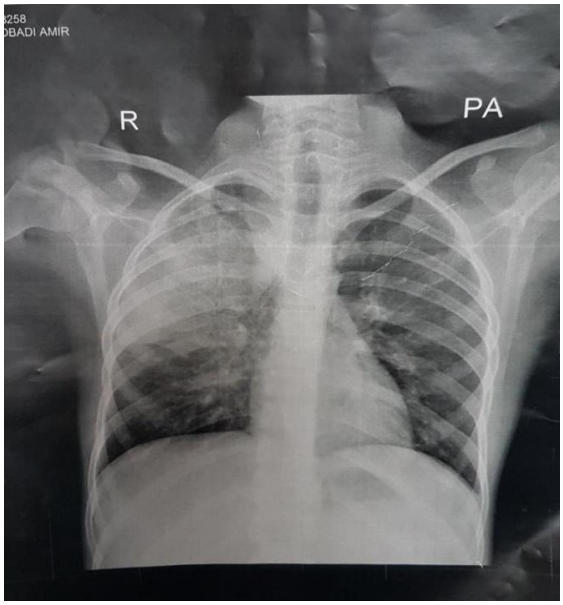

Fig. 1: First chest X-ray

PCR serology for COVID-19 was performed for him and it was negative. All laboratory data are seen in **Table 1**. IGRA and sputum smear was taken from the patient for tuberculosis assessment and the smear was negative but IGRA was positive. Lung CT scan was done and there were airspace consolidations in the right upper lobe and right middle lobe associated with ground glass opacities and interstitial septal thickening. Multifocal parenchymal nodules and nodular consolidations are also depicted in the rest of both lungs. Mild right pleural effusion and enlarged lymph nodes in right hilum and subcarinal region were seen (**Fig. 2**).

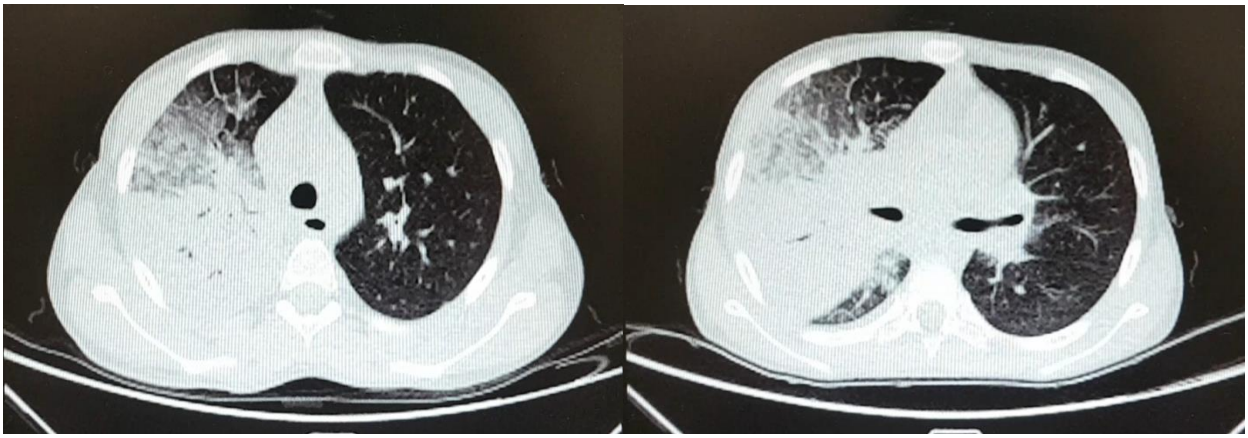

Fig. 2: Lung CT scan

Table-1: Laboratory data

lab data(unit)	first- follow up	lab data(unit)	first- follow up	lab data(unit)	first- follow up
RBC (normal range: 4.7 to 6.1 *10^6)	3.5-5.5				
WBC (normal range: 4-10*103/ml)	4.19-2.26-1.92-4.2	PBS	NEG	Immunology	NL
Pmn	2910-1600-1450	Ig G,M.E.A	NL	NBT	100%
Lymph (normal range0.8-4*103/ml)	860-540-370	CH 50	NL	Trop I	NL
Hb (normal range: 11-16 g/dL)	12.3-11.1-11.5-11.3	BM Acid fast	NEG	CK-MB	NL
Plt(normal range: 150-450*10^4/ml)	98-53-62	Flocytometry	NL	Pro BNP-NT	NL
Bun(normal range: 3-12 mg/dL)	16-7	Urine VMA	NL	CPK(normal range: 195-700 U/L)	38
Cr(normal range:	0.8-0.5	-	-	CK-MB	9 (NL)

0.47-1.05 mg/dL)				(normal range: 0-24 U/L)	
LDH (normal range: 60 to 170 units/L)	970	Sputum acid fast	NEG	Ani CCP	NL
Ast	45-49	IGRA	Positive	RF	NEG
Alt	38-23	-	-	DAT	NEG
Alb(normal range: 3.5-5.2 g/dL)	2.9-3.2	HIV Ab	NEG	K 39	NEG
CRP	34-21	EBV	NEG	IFA	NEG
ESR	31-45	SARS covid 19 IgM	Neg	Wright	NEG
PT(normal range: 11-14 sec)	13.4	SARS covid 19 IgG	Neg	2ME	NEG
INR (normal range: 0.9-1.1)	1	CD4	36	Widal	NL
PTT (normal range: up to 65 sec)	43	CD8	40	-	-
Uric Acid	4.2	BAL			-
U/A SG: 1021 WBC: 2-3 Protein: NEG		-	WBC	63	-
		-	Poly	80	-
		-	Lymph	18	-
U/C	NEG	-	BAL-Fungus-Culture	NEG	-
B/C	NEG	-	BAL Culture	Pseudomonas aeruginosa	-
Ferritin	2800	-	Anaerobic culture	NEG	-
Fibrinogen	500	MTB PCR	NEG	-	-
D Dimer	7.94 (negative< 1)	MTB Smear	NEG	-	-
CPK (normal range < 6)	41	CMV PCR	NEG	-	-
VitD	14	COVID 19 PCR	NEG	-	-
PCR COVID 19	NEG	-	-	-	-
Ca(normal range:7-12 mg/dL)	7.3-7-8	-	-	-	-
P(normal range: 3.5-5.0mg/dL)	3.5-3.3.6	-	-	-	-
Mg(normal range:1.2-2.6 mg/dL)	1.3-1.6	-	-	-	-
Na(normal range: 133-146 mmol/L)	128-131	-	-	-	-
K(normal range: 3.2-5.5 mmol/L)	4.2-3.9	-	-	-	-

Broncho alveolar lavage (BAL) was done. Its result was the mycobacterium sensitive to Rifampin in PCR. Tuberculosis (TB) treatment protocol with four drugs and antibiotics including Vancomycin and Meropenem were administered for him but despite this treatment, he had a high-grade fever, and echocardiography was performed showing coronary artery ectasia (the size of the RCA was 2.8mm and LAD was 3.4mm) (**Fig. 3**).

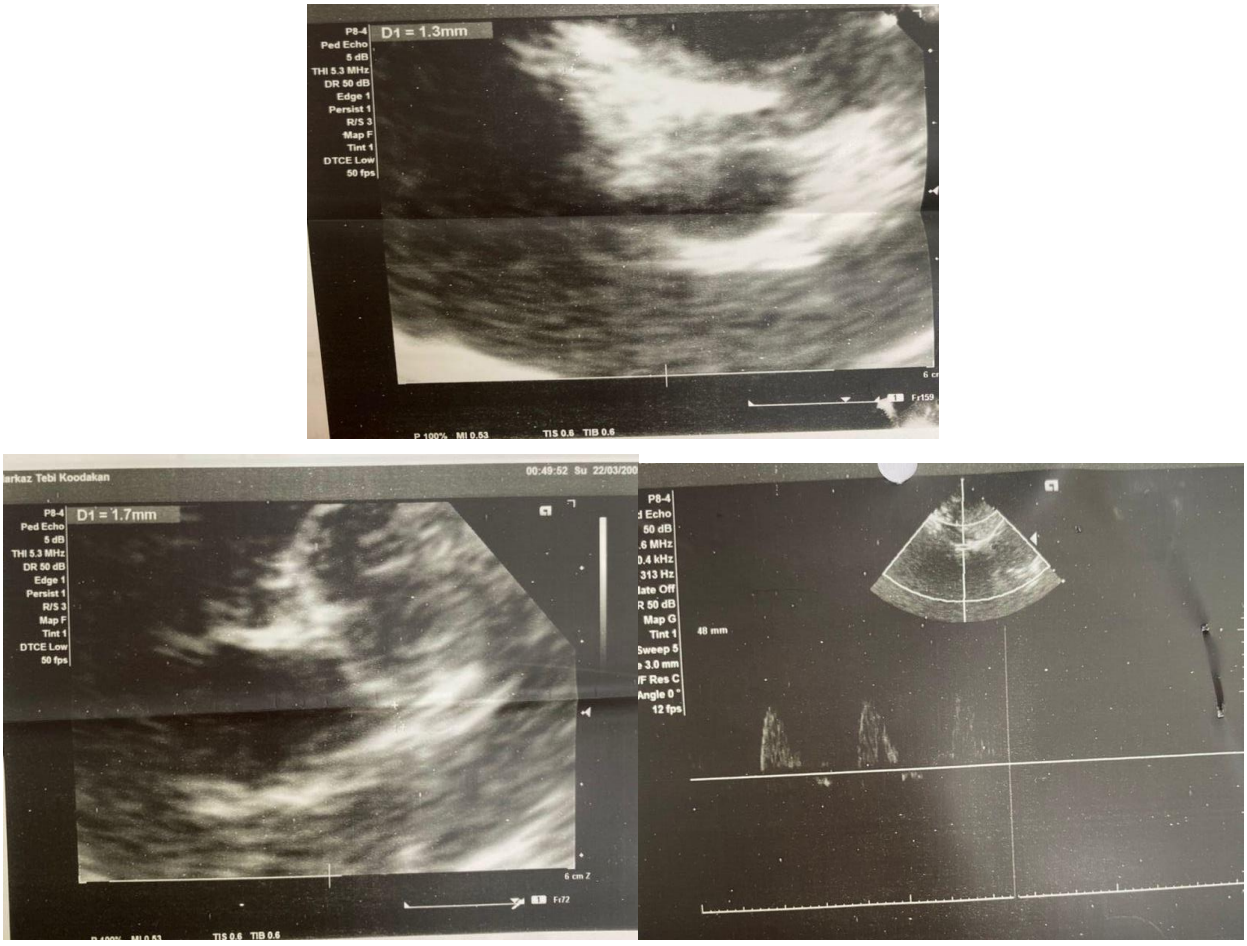

Fig. 3: Echocardiographic images

Because he had high levels of inflammatory factors such as D-dimer =7.94 (neg<1) and lymphopenia, we were suspicious of TB activation following COVID-19 involvement in the past. After a rheumatologic consult, IVIG was administered for him. Although TB treatment and IVIG were continued for 2 weeks and also antibiotics were changed to Cefepime and Cloxacillin, the fever continued. Then methylprednisolone pulse (30 mg) was started for him and with this treatment, fever became fewer but not discontinued and pancytopenia flow was worsened. Further workups continued. Due to the patient's situation, pediatricians were suspicious of HLH (Hemophagocytic lymphohistiocytosis) involvement in this child, and Naproxen (250 mg TDS) and methylprednisolone were added to his treatment chart. Fever was controlled with this plan and his general appearance

became better and after 2 months of admission, he was discharged with oral drugs.

When he was at home, his fever increased and he was referred to our hospital again. He was admitted again and we found high-grade fever and cytopenia. We came to the possibility of drug-resistant TB for him and after adding streptomycin, levofloxacin, IGRA, sputum smear, and BAL, we observed that all tests were negative for TB but pseudomonas aeruginosa was seen in BAL. Bone marrow Aspiration and biopsy (BMA/BMB) were also done, bone marrow was normal without any evidence of malignancy. Because these tests were negative and chest X-ray showed better changes (**Fig. 4**), we concluded that TB was treated and Amikacin + Levofloxacin were added to pseudomonas aeruginosa treatment, but still there was a high-grade fever.

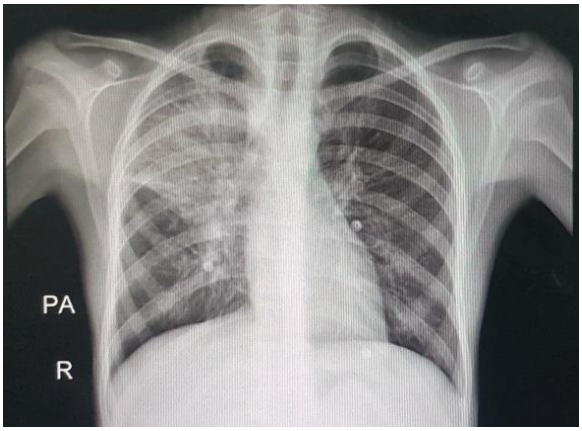

Fig. 4: Post TB treatment chest X-ray

Bone marrow aspiration, bone marrow biopsy, abdominal and lung CT scan were done for him. Abdominal CT scan was normal but in the lung CT scan collapse consolidation in posterior right upper lobe segment and lateral right middle lobe segment, ground glass opacity, increased interlobular septal thickness, and ground glass nodules was seen in apical segment of right upper lobe and medial segment of right middle lobe. Also, mediastinal lymphadenopathy was observed in the right para tracheal of the right hilum (**Fig. 5**).

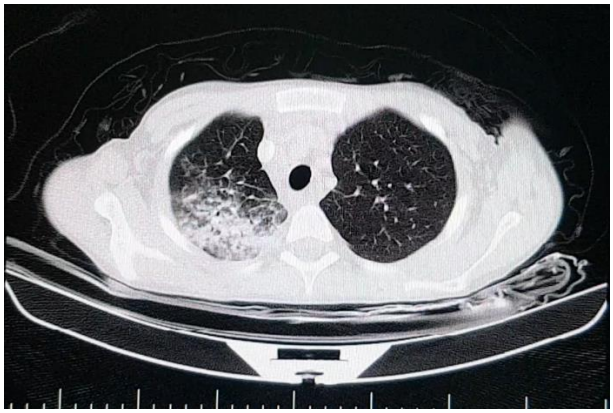

Fig. 5: Lung CT scan

Neuroblastoma and immunologic disorders (due to lymphopenia) were evaluated but nothing was found. The patient was evaluated for autoimmune lymphoproliferative syndrome (ALPS). Vitamin B12 level and double-negative T-cell were also checked. Double-negative T-cell was negative but vitamin B12 was elevated. Because he received multivitamins, this supplement was discontinued but in the second blood vitamin B12 level assessment, it was high again. In this time, the patient was discharged with self-consent.

At home, he experienced severe edema in extremities, abdominal bulging, and enlarged neck size. He referred to our hospital again and we found hepatosplenomegaly (**Fig. 6**), ascites, 4 plus edema in all extremities, cervical lymphadenopathy, and a few bilateral pleural effusions that worsened during the time. Methylprednisolone pulse was started for him again.

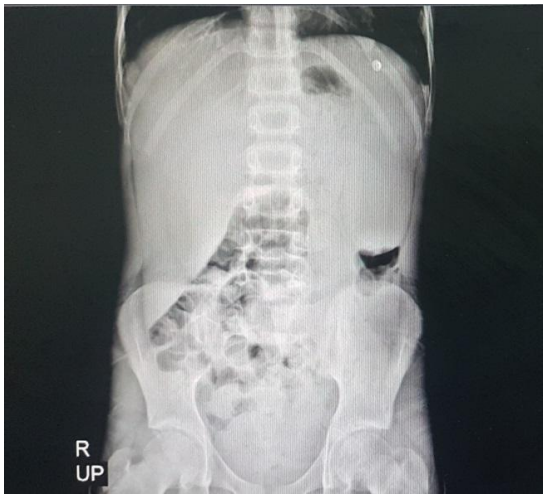

Fig. 6: Abdominal X-ray

A wide spectrum antibiotic was administered and an excisional biopsy was performed from the cervical lymph node. A pathological assessment was done and its result showed Anaplastic large cell lymphoma, ALK positive (ALK+ ALCL) (**Fig. 7**). The IHC (Immunohistochemistry) report was a positive immunoreaction for CD30, ALK, CD4, and CD43. It showed a negative immunoreaction for CD20, PAX5, CD3, CD8, CK and synaptophysin.

The patient expired before starting treatment, unfortunately.

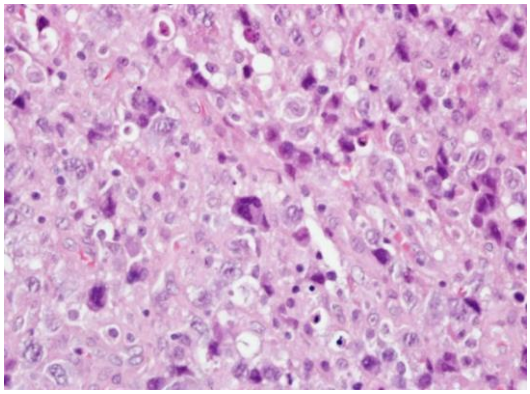

Fig. 7: Pathological feature of ALK+LBCL

3- DISCUSSION AND CONCLUSION

In this report, we represented a complicated case of TB with ALK+ ALCL. TB and ALK+ALCL had pulmonary manifestations in this case, making a complicated situation for diagnosis. As previously mentioned, the first doubt about the patient was TB and it was true because his TB evaluations were positive but after treatment, his manifestations became worsened or remained. He experienced high-grade refractory fever. Most ALK+ALCL (50–70%) cases have peripheral, mediastinal, or abdominal lymphadenopathy. B symptoms (fever, night sweats, and weight loss) are common in patients (54–75%), and extranodal involvement is common (approximately 60% of cases). The skin (8–21%), soft tissue (17–21%), lung (6–13%), liver (3–17%), bone (12–17%), and spleen (8–21%), as well as bone marrow (0–16%) are the most often detected extranodal locations. The B symptoms are seen in TB and in the ALK+ ALCL. It can make physicians confused and also less than 15% of patients have lung involvement in ALK+ ALCL (7-13). In the laboratory study, elevated lactate dehydrogenase (LDH), thrombocytopenia, and anemia are seen in less than 40% of patients (8). Our patient had high level LDH, and thrombocytopenia but anemia didn't occur in him.

About 70% of ALK+ ALCL patients with lung involvement are lower than 18 years (15).

This is a rare disease and some cases are involved with HIV. In fact, AIDS can be associated with ALK+ ALCL and it should be considered (16, 17). In our case, HIV testing was performed and it was negative. When a patient with active TB doesn't respond to its treatment protocol, there are some causes other than MDR-TB, such as drug compliance, or involving HIV or undiagnosed malignancy. In these cases constitutional symptoms persist after the treatment (18, 19).

There are very few cases with TB and ALK+ ALCL in the world. Coexistence of pulmonary TB and lung involvement of ALK+ ALCL made us confused (20, 21).

In our patient CD30, ALK, CD4, and CD43 were positive in the IHC test. These markers, especially CD30 and ALK are the key markers for ALK+ ALCL diagnosis (22). There are several patterns of ALK+ ALCL and there are some factors which can help differentiate the patterns of ALK+ ALCL. For example, in the small cell pattern, expression of CD30 + ALK is a hallmark. CD4 positivity is also most commonly observed in the patients with large T-cell lymphoma (23, 24).

Our patient didn't have lymphadenitis when he was referred to our hospital and his complaint was respiratory disorders from a long time ago. During evaluations,

refractory fever and pulmonary involvement were the main patient's problems and it is important in patients with these manifestations along with positive TB tests and no response to treatment, that the underlying ALK+ ALCL be considered.

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