

## Case Report

# ALK-positive anaplastic large cell lymphoma with multifocal bone involvements: a case report and review of the literature

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**Abstract:** Anaplastic large cell lymphoma (ALCL) is a rare disease characterized by the infiltration of pleomorphic cells and expression of Ki-1 or CD30 antigen. ALCL, usually involves with lymph nodes, also with skin, liver, lung, soft tissue, and bone marrow, but bone involvement is rare. We reported a 16-year-old boy presented with an eight-month history of pain in his dorsal spine and with late one-month history of ache in his left articulatio coxae accompanied with the limitation of motion. CT and MRI scans reported the bone destruction in the left iliac bone, thoracic vertebra 11, 12, lumbar vertebra 1-4, and sacral vertebra. A seriously squeezed 1st lumbar vertebra was also observed. By the second biopsy of left iliac bone, ALK (anaplastic lymphoma kinase) positive ALCL was diagnosed. The patient responded well to the DHAP chemotherapy. In conclusions, ALCL can present with multiple or solitary bone involvement, meticulous examination of initial and repetitive biopsy is recommended to make an accurate diagnosis of ALCL. Suitable chemotherapy should be adopted after diagnosis.

**Keywords:** ALK-positive, anaplastic large cell lymphoma, multifocal bone involvement, bone involvement

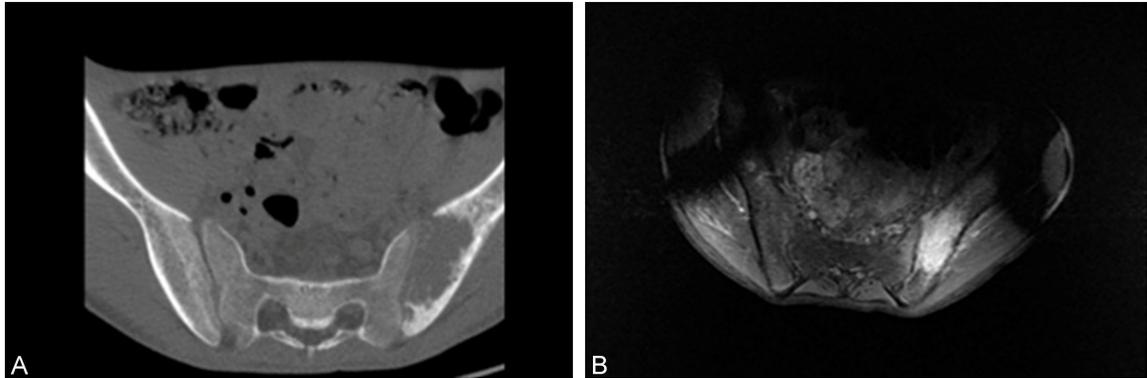
## Introduction

Anaplastic large cell lymphoma (ALCL) was first described by Stein in 1985 [1]. It is a rare disease accounting for estimated 10-15% of all non-Hodgkin lymphomas (NHL) in children and 1-2% in adults [2]. It is characterized histopathologically by the infiltration of pleomorphic cells and expression of Ki-1 or CD30 epithelial membrane antigen and the interleukin-2 receptor [3, 4]. Depending on the expression of the aberrant anaplastic lymphoma kinase (ALK), ALCL could be categorized into two types, namely ALK-positive and ALK-negative sub-classes [5]. The predominant presenting symptom of ALCL is lymph node involvement in peripheral intra-abdominal or mediastinal. Additionally, ALCL has also been reported to involve skin, liver, lung, soft tissue, and bone marrow [2]. But the involvement of bone is rarely described. Here, we report a case of ALK-positive ALCL with prominent bone involvement in a 16-year-old boy.

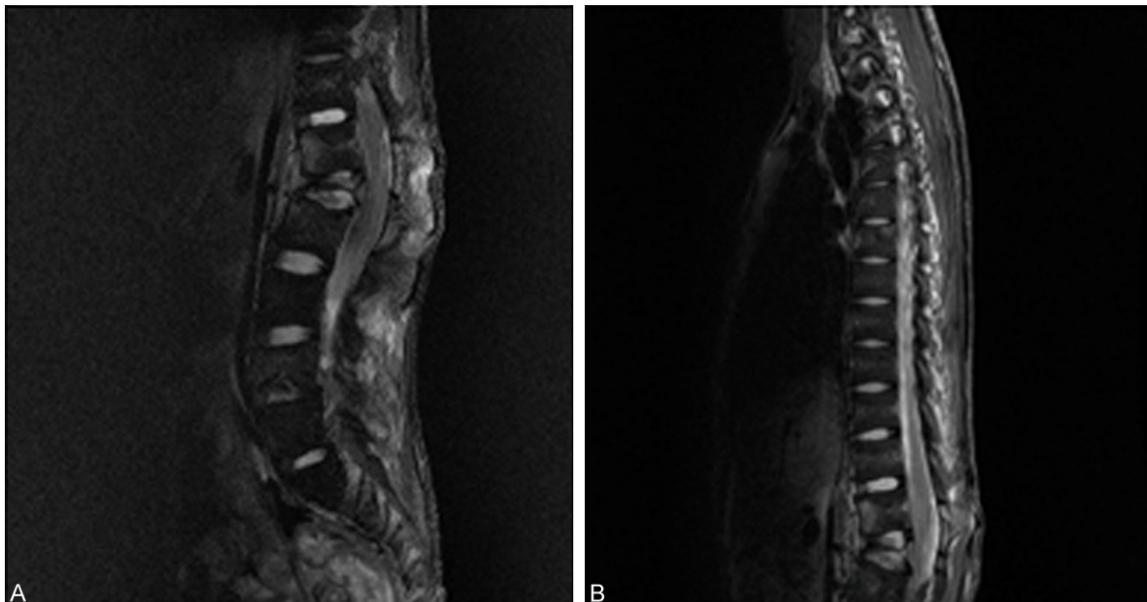
## Case report

A 16-year-old boy presented with an eight-month history of pain in his dorsal spine and with a late one-month history of ache in his left articulatio coxae accompanied with the limitation of motion. After suffered from pain in abdomen for five days, he was admitted to our hospital on May 5<sup>th</sup>, 2016. Physical examination revealed a right scoliosis, besides the tenderness in the abdominal vertebra and left the hip joint. Meanwhile, he had a lymphadenopathy in the neck and right axillary. The serious whole abdominal tightness with rejection to touch was observed. No fever, cutaneous lesions, hepatomegaly or splenomegaly was found. Laboratory tests showed elevated CRP (C-reactive protein) of 87.6 mg/L and ESR (Erythrocyte sedimentation rate) of 66.0 mm/h. EBV (Epstein-Barr virus) DNA (deoxyribonucleic acid) was elevated to 1.76E+01 copies/mL. HLA-B27 was negative, and the serum LDH (lactate dehydrogenase) level was within normal range. CT

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**Figure 1.** A bone destruction with measuring 4.3×1.8 cm in the left iliac bone in CT (A) and MRI (B).

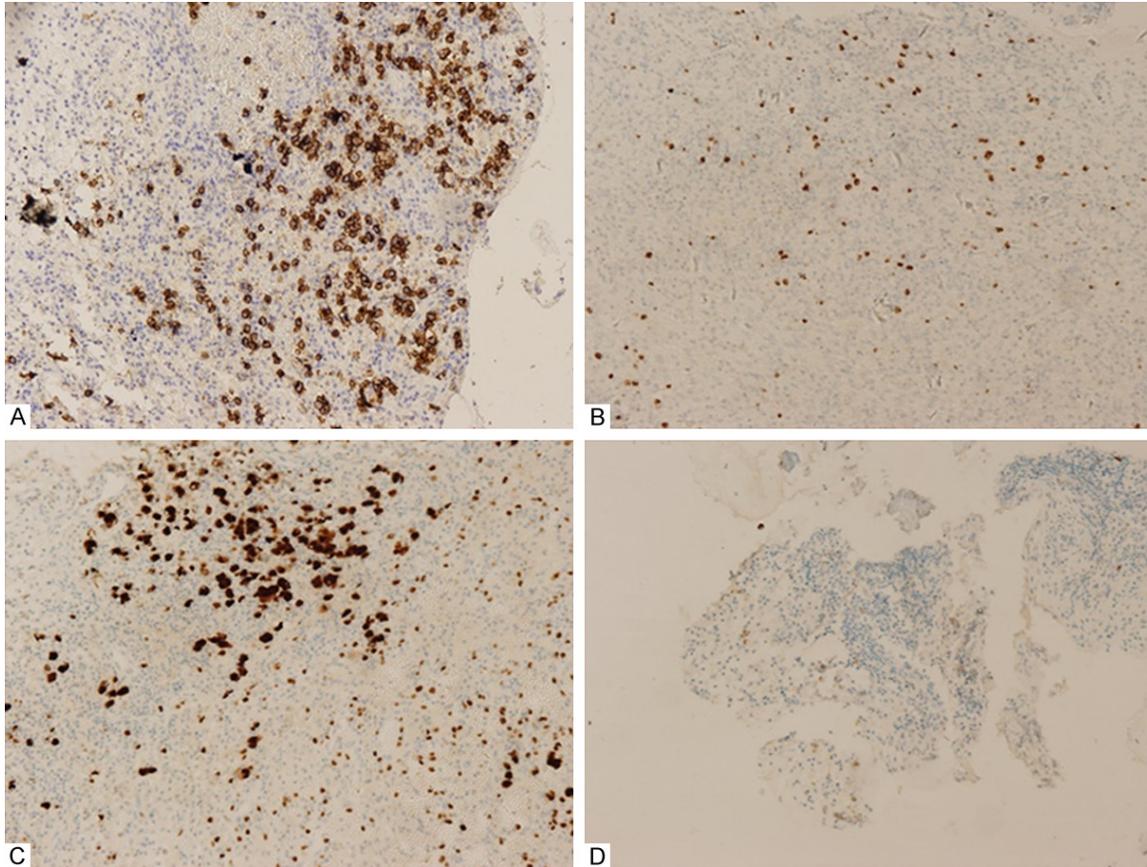


**Figure 2.** Serious compression of the 1st lumbar vertebra (A) and various bone destructions in vertebrae (B) in MRI scan.

(Computed Tomography) and MRI (Magnetic Resonance Imaging) scans reported a bone destruction with measuring 4.3×1.8 cm in the left iliac bone, surrounded by sclerotic bones and swelling soft tissues (**Figure 1**). There were also various apparent bone destructions in thoracic vertebra 11, 12, lumbar vertebra 1-4, and sacral vertebra. Especially, the 1st lumbar vertebra was seriously squeezed (**Figure 2**). In addition, abdominal CT just found some enlarged retroperitoneal lymphoid nodes and a mild splenomegaly. The lymph node biopsy in the neck was performed, and only reactive hyperplasia was observed. An ultrasound-guided fine needle aspiration biopsy of left iliac bone was nondiagnostic.

Subsequently, the left flank bone was surgically partially resected. The following pathological examination revealed that effacement of normal architecture by granulomatous tissues and mixed cells including lymphocytes, eosinophil granulocytes, plasma cells in which there were a few large atypical cells with one-nucleoli mostly and double-nucleoli sparingly. Immunohistochemically, these cells were positively stained with CD30, Ki-67, ALK-1 (anaplastic lymphoma kinase-1), GB and EMA (epithelial membrane antigen) but negatively with CD45, CD15, mum-1, PAX-5 (**Figure 3**). There was no morphological evidence of lymphoma infiltration according to the bone marrow biopsy. Thus, diagnosis of ALK-positive ALCL was decided

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**Figure 3.** Immunohistochemistry of bone biopsy. A: CD30, 100X magnification; B: Ki-67, 100X magnification; C: ALK-1, 100X magnification; D: EMA, 100X magnification.

histopathologically. The patient was then treated with a combination of dexamethasone, high-dose ara-c and platinum (DHAP). Eventually, the desired with full remission was obtained, the total hospitalization lasted 88 days. He is now in our regular follow-up with no recurrence to date.

### Discussion

ALCL is characterized by the cohesive proliferation of large pleomorphic cells expressing CD30 (Ki-1), and commonly involves the lymph nodes, as well as a wide variety of extranodal sites such as skin, soft tissue, lung while primary or secondary involvement of bone is rare [6, 7]. In clinical practice, the presence of bone involvement in non-Hodgkin lymphoma is uncommon, the numerous osteolytic lesions usually lead to the considering of metastatic carcinoma or multiple myeloma. In this setting, the diagnosis of ALCL seems to be more complicated because of the rare incidence and less common presentation of bone involvement.

We also did a literature review summarizing the characteristics of ALK-positive ALCL with bone involvement. 14 publications were obtained from a comprehensive search in Pubmed from 2006 to 2016 [8-19]. In total, 15 cases including the current one were analyzed. The median age at presentation was 21 (3-52) years, and 11 (73.3%) of them were males. The median disease duration described in 13 cases was 4.5 months. The pain as the initial and main symptom was presented in 12 (80%) patients at the incipient stage of the disease. Half of the patients (7/14) experienced a fever. Among all the cases, nine patients (60%) had nodal affected in addition to bone involvement. Meanwhile, 11 (73.3%) cases were found to have multiple bone sites involved in contrast to only 4 cases (26.7%) had solitary bone affected. Most patients (66.7%) did not suffer the hepatosplenomegaly. Splenomegaly was found in 5 (33.3%) cases and hepatomegaly in 2 (13.3%) cases, respectively. The presence of bone marrow involvement was observed in 77.8% (7/9)

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**Table 1.** Characteristics of ALK positive ALCL patients with bone involvement from 2006 to 2016

Time	Author	Sex	Age (yrs)	Course (months)	Fever	Skin lesions	Primary symptoms	Extent of disease	Pattern of bone disease	Hepato-sple-nomegaly	LDH	BM	Immuno-phenotype	Method of diagnosis	Treatment	Prognosis
	Our patient	M	16	8	N	N	Pain in dorsal spine and left hip	LN, bone	Multifocal	Splenomegaly	WNR	N	ID	Repeated biopsy of bone	DHAP	Remission
2016	Chen, et al [8]	M	13	8	Y	N	Pain in waist, fever	LN, bone	Multifocal	Both	high	N	T	Soft tissue biopsy	Hyper-CVAD/MA, AHST	CR (24 months)
2016	Kim, et al [19]	F	52	2	Y	N	Pain in multiple areas, fever	Bone	Multifocal	N	WNR	NG	Null	Repeated biopsy of soft tissue	CHOP	CR (5 months)
2015	Chen, et al [9]	F	40	4	Y	N	Pain in left hip, fever	LN, bone	Multifocal	Both	WNR	N	Null	Bone biopsy	Hyper-CVAD/MA	CR (24 months)
2015	Gajendra, et al [10]	F	14	2	N	Y	Pain in left sided chest, weight loss, difficulty in breathing	LN, bone	Multifocal	Splenomegaly	WNR	N	Null	Lymph node biopsy	CHOP	NG
2013	Nayak et al [11]	M	50	3	N	N	Intermittent chest pain, fatigue, weight loss	Bone	Multifocal	N	high	N	T	Biopsy of soft tissues and bone	CDVP	NG
2012	Mika, et al [12]	M	13	NG	Y	N	Pain in both hips and left leg	Bone	Multifocal	N	NG	N	T	Bone biopsy	NG	NG
2012	Khor, et al [13]	F	26	6	Y	N	Neck pain, fever, cough and weight loss	LN, bone	Multifocal	Splenomegaly	WNR	NG	T	Bone biopsy	NG	NG
2010	Smith, et al [14]	M	23	2	Y	N	Fever, night sweats, weight loss, left upper extremity weakness and paresthesia	LN, bone	Multifocal	N	NG	NG	T	Bone biopsy	CHOP	CR (12 months)
2007	Rahmat, et al [15]	M	26	2	Y	N	Pain and swelling of left jaw	LN, bone	Multifocal	N	NG	NG	ID	Biopsy of bone and soft tissues	NG	CR
2007	Ng, et al [16]	M	13	1.5	N	N	Pain and stiffness of right shoulder	LN, bone	Solitary	N	WNR	NG	Null	Bone biopsy	ALCL199	CR (20 months)
2006	Mounasamy, et al [17]	M	8	3	N	N	Pain in right upper extremity	Bone	Solitary	N	NG	N	T	Soft tissue biopsy	NG	Not well
2006	Bakshi, et al [18]	M	3	0.33	N	N	Pain in left buttock and lower extremities	Bone	Multifocal	N	high	Y	Null	Soft tissue biopsy	VPC	CR
		M	9	NG	NG	Y	Lytic lesion of the right proximal femur	Bone	Solitary	N	NG	Y	Null	Bone biopsy	DECCL	Died after 1 year
		M	14	1	N	N	Left-side chest wall mass	LN, bone	Solitary	N	WNR	NG	T	Biopsy of lymph node and soft tissues	CMOP	CR (132 months)

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patients. After treatment, 81% (9/11) cases maintained apparent remissions. One patient died of progression, and one didn't respond to the therapy well. The details of all 15 cases were summarized in **Table 1**.

Only 2 of 15 patients were diagnosed accurately by repetitive biopsies. In contrast, most of them had a long diagnosis process, and some cases were initially misdiagnosed as other diseases like tuberculosis (TB), eosinophilic granuloma and so on. Those misdiagnoses might be most likely due to that the presence of lytic bone lesions usually lead physicians to first consider TB, metastatic carcinoma, multiple myeloma and osteomyelitis. In this patient, the compression of lumbar vertebra misled us to make the diagnosis of eosinophilic granuloma. The histopathological characteristic of ALCL is the constitution of large plastic cells with round or pleomorphic nuclei. The histopathological characteristic of ALCL is the constitution of large plastic cells with round or pleomorphic nuclei. The most valuable marker for ALCL diagnosis is CD30, which were positive in all the 15 cases we analyzed. About 60% of them express T cell-associated antigens, such as CD3, CD43 or CD45RO, in which cytotoxic granule proteins are often present [20]. Therefore, it is suggested that the diagnosis of bone ALCL should be based on histopathology and immunohistochemistry (IHC) [21]. It is important to make a trustworthy histologic examination with early biopsies, and it is also suggested to perform a biopsy in the involved soft tissue rather than bone tissue because the decalcification process of bone tissue could affect the IHC result [12, 13].

Usually, ALK-positive ALCL has favorable prognosis. Studies have demonstrated that the response of ALCL to chemotherapy is desirable, the remission rate ranges from 60%-90% [22-24]. However, there is still no consensus about the prognosis of the bone involved ALCL. Most of the cases in our literature review observed relatively good responses to the treatment, however, conversely, two cases showed a poor prognosis [12, 25]. To date, no evidenced risk factor has been evidenced for ALCL progression. It is reported that the infection of Epstein-Barr virus (EBV) plays an important role in the pathogenesis of ALCL [26]. In our case, the patient was tested positively for EBV infection. Other researches proposed that the presence

of mediastinal disease and visceral or cutaneous involvement might have predictive value [27]. In addition, histological features, such as presence of a lymphohistiocytic or small cell component, positive PCR for NPM1-ALK in peripheral blood or bone marrow, low anti-ALK antibody titers and detection of minimal residual disease (MRD) might also predict worse outcome [28-32].

In conclusion, ALCL can present with multiple or solitary bone involvement. In clinical practice, lymphoma is an important differential diagnosis when the bone is involved. A meticulous examination of initial and repetitive biopsy is recommended to make an accurate diagnosis of ALCL. As soon the diagnosis is confirmed, suitable chemotherapy should be adopted.

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### Disclosure of conflict of interest

None.

### Abbreviations

ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; M, male; F, female; Yrs, years; Y, yes; N, no; WNR, within normal range; NG, not given; LN, lymphoid node; BM, bone marrow; ID, indeterminate; CR, complete remission; LDH, lactate dehydrogenase; DHAP, dexamethasone, high dose ara-c and platinum; hyper-CVAD/MA, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone/methotrexate and cytarabine; AHSCT, autologous hematopoietic stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CDVP, cyclophosphamide, doxorubicin, vincristine and prednisone; ALCL199, dexamethasone, methotrexate in combination with ifosfamide, cytarabine, etoposide which alternated with cyclophosphamide and doxorubicin; VPC, vincristine, prednisone and cyclophosphamide; DECAL, dexamethasone, etoposide, cytarabine, cisplatin and L-asparaginase; CMOP, cyclophosphamide, vincristine, methotrexate and prednisone.

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