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Case report

Inflammatory myofibroblastic tumor of bone harboring an *ALK* gene amplification

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ABSTRACT

Inflammatory myofibroblastic tumor (IMT) is a neoplastic proliferation of myofibroblastic/fibroblastic cells with a variable admixture of inflammatory cells. It primarily affects soft tissue and viscera of children and young adults. IMT occurring in bone is extremely rare. Approximately 50% of IMTs carry a clonal rearrangement of the anaplastic lymphoma kinase (*ALK*) gene, while other receptor tyrosine kinase gene rearrangements have been seen in a small subset of IMT. Herein, we report the first case of IMT which harbors an *ALK* gene amplification rather than a rearrangement thus resulting in overexpression of the protein, arising from the femur of a 24-year-old man. Our case provides a novel pathogenesis for IMT. An overview of cytogenetic abnormalities of IMT is also integrated into this report.

1. Introduction

Inflammatory myofibroblastic tumor (IMT), previously known as inflammatory pseudotumor, is a distinctive neoplasm composed of myofibroblastic/fibroblastic cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and eosinophils. The tumor has an intermediate biologic potential characterized by locally aggressive behavior, frequent recurrence and rare metastases. IMT can occur at any age, but has a predilection for children, adolescents and young adults, with estimated 150–200 new cases diagnosed annually in the United States [1]. The tumor affects primarily soft tissue and visceral organs. The most frequent sites of involvement are mesentery, omentum, retroperitoneum, pelvis, and abdominal soft tissues followed by the lung, mediastinum and the soft tissue of the head/neck region. IMT occurring in bone is extremely rare; however, it may affect any skeletal site, including the long [2,3] and flat [4,5] bones, as well as the axial [6–8] and craniofacial [9–12] skeleton. Thus, it is important to include IMT in the differential diagnosis in working up a spindle cell lesion of the bone, especially in a needle biopsy.

Approximately 50% of IMTs harbor a clonal rearrangement of the anaplastic lymphoma kinase (ALK) gene on the short arm of chromosome 2 (2p23), leading to the formation of a chimeric fusion protein which can be detected by immunohistochemistry [13]. Interestingly, 90% of fusion-negative IMTs were seen in adults, whereas more than 90% of pediatric IMT showed gene rearrangements [14]. Furthermore, "ALK-negative" IMTs may be more aggressive, with a higher frequency of metastasis [1]. Other receptor tyrosine kinase gene rearrangements have also been reported, including those involving ROS1, PDGFRβ, NTRK3, and RET [14–16]. Herein, we report an IMT of bone demonstrating ALK gene amplification. To our knowledge, this is the first reported case of IMT harboring a clonal ALK amplification, thus providing a novel pathogenesis for this neoplasm.

2. Case report

The patient, a 24-year-old man, presented with a pathologic fracture of his right femur. His past medical history was remarkable for right thigh surgery for a diagnosis of 'myositis ossificans' at an outside hospital seven years prior to the presentation. He reported that he was unable to bend his right knee since childhood. Conventional radiographs showed an oblique mildly comminuted fracture of the right mid femoral diaphysis through an aggressive radiolucent lesion (Fig. 1 A). The mass appeared to be centered at the level of the cortex, with a soft tissue component. A magnetic resonance imaging (MRI) scan of the right femur revealed a 8.3 x 6.9 cm mass corresponding to the area of destruction on the radiographs that extended into the medial and anterior soft tissues of the thigh (Fig. 2 B&C). This lesion was T1 hypointense and heterogeneously T2 hyperintense. Extensive periosteal

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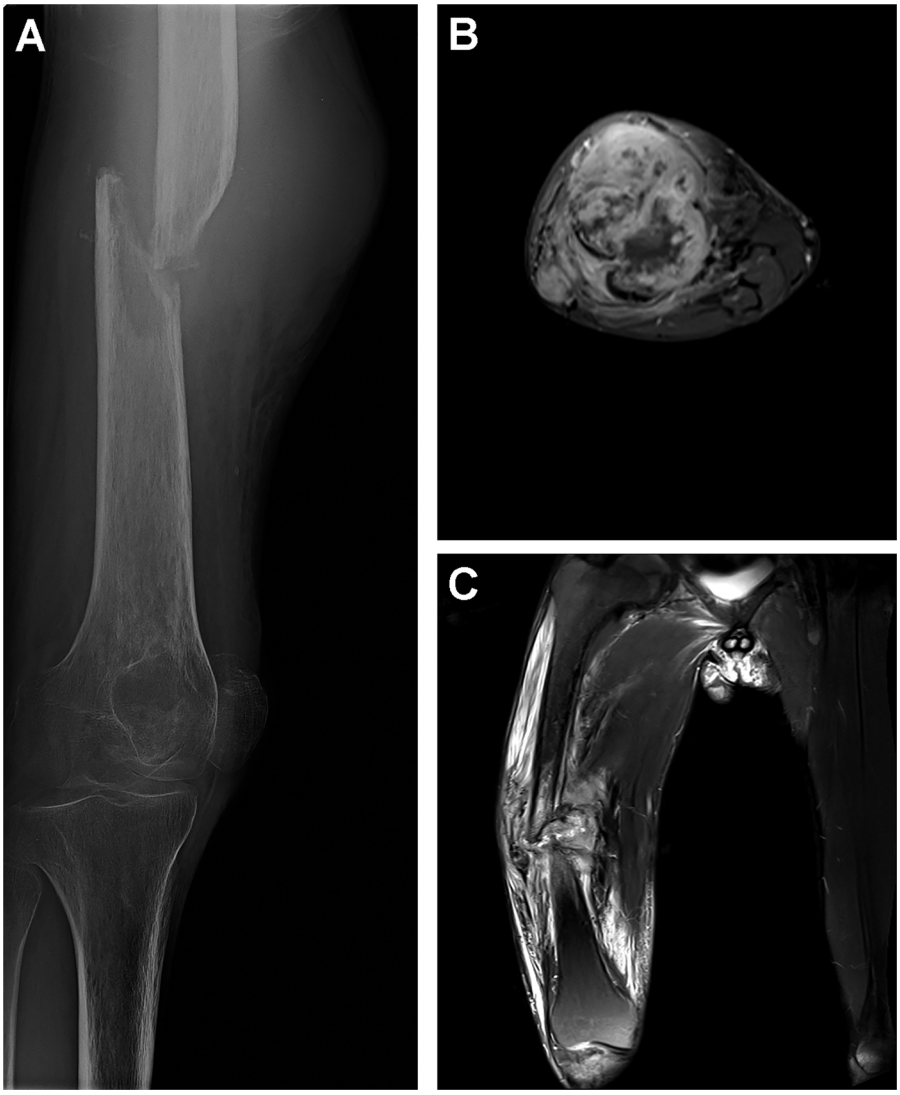

Fig. 1. Imaging studies of the right femur. A, conventional radiograph demonstrated an oblique mildly comminuted fracture of the right mid femoral diaphysis through an aggressive radiolucent lesion. B and C, fat saturated, turbo spin echo magnetic resonance imaging of the right femur. The axial (B, T1-weighted) and coronal (C, T2-weighted) images revealed a mass corresponding to the area of destruction on the radiographs that extended into the soft tissue. This lesion was T1 hypointense and heterogeneously T2 hyperintense.

thickening and edema were noted proximally. Physical examination revealed a firm, large soft tissue mass in the anterior thigh and a right knee immobilizer in place.

The patient underwent an open biopsy of the right thigh mass. The histologic sections showed a proliferation of low-grade, variably cellular, spindle cells admixed with abundant lymphoplasmacytic cells. The spindle cells were diffusely immunoreactive for smooth muscle actin (Bond™, PA0943, prediluted) and ALK (Ventana, D5F3, prediluted), but negative for desmin (Ventana, NCL-DE-R-11, prediluted), S-100 protein (Ventana, 760–2523, prediluted) and Pan cytokeratins (Ventana, 760–2135, prediluted) (Fig. 2). Thus, a diagnosis of IMT was rendered. All immunohistochemical stains were performed using Ventana (Roche Diagnostics, USA) or Bond (Leica Biosystems Inc., Buffalo Grove, Illinois, USA) automatic platform, respectively.

Given that an ALK gene rearrangement is the most frequent molecular genetic abnormality in IMT, a dual-color, break-apart fluorescence in-situ hybridization (FISH) for ALK was subsequently performed on a non-decalcified tissue section, utilizing the Vysis ALK Break Apart FISH Probe Kit (06N38-020, Abbott Laboratories, Abbott Park, Illinois, USA). Interestingly, while no ALK gene rearrangement was identified, an unequivocal clonal ALK gene amplification was detected (Fig. 3).

The patient subsequently had an excision of his right thigh mass and open reduction and internal fixation. His postoperative course was uneventful at the 8-month follow up point.

3. Discussion

Primary IMT of bone is extremely rare but may involve any skeletal site, with a wide age distribution, ranging from 10 months to 75 years. Femur and temporal bone are the most common sites for long and craniofacial bone involvement, respectively [2,3,17], while it can rarely affect flat bones such as ilium [4] and scapula [5], and the axial skeleton including cervical and lumbar spines [6,7], and sacrum [8]. All cases affecting a long, tubular bone reported to date have occurred in young to middle-aged adults. The vast majority of patients presented with pain and/or soft tissue swelling, whereas hearing loss was the most common presenting symptom in patients with lateral skull base involvement [17]. Interestingly, a paraneoplastic syndrome, including inflammatory dorsalgia and polyarthralgia, anemia, thrombocytosis, and paraneoplastic pemphigus, may be the first sign of primary or metastatic IMT, which was further confirmed by the disappearance of the clinical symptoms after surgical resection [8,18–20].

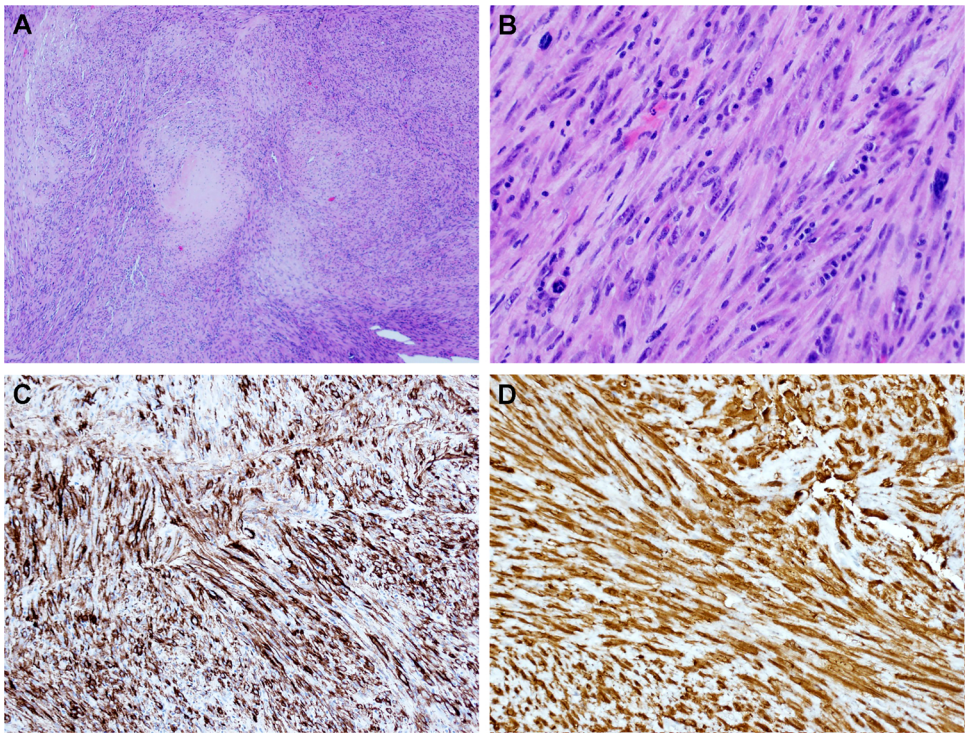

Fig. 2. Histologic features and immunophenotype. A low power view of hematoxylin and eosin-stained section revealed a low-grade, variably cellular, spindle cell proliferation (A). At higher magnification, the lesional cells exhibited mild nuclear pleomorphism, with occasional large, hyperchromatic nuclei, and were admixed with abundant lymphoplasmacytic cells (B). The spindle cells were diffusely immunoreactive for smooth muscle actin (C) and ALK (D). Original magnification x40, x200, x100, x200, respectively.

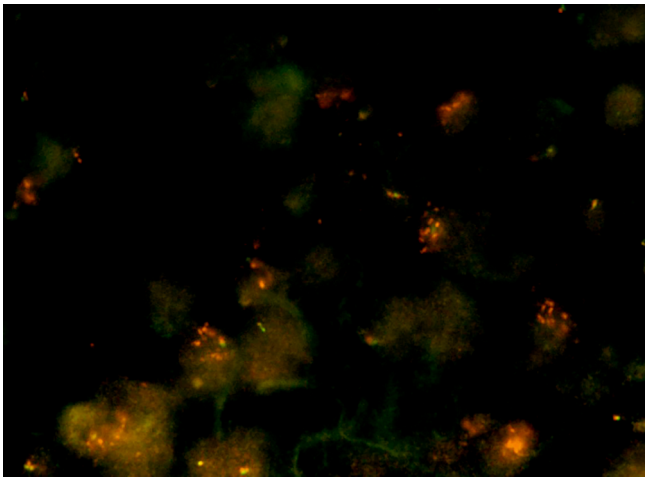

Fig. 3. Fluorescence in-situ hybridization (FISH) of an *ALK* gene rearrangement. The Vysis LSI ALK Dual Color Break Apart FISH Probe is a mixture that consists of two fluorophore-labeled DNA probes: Vysis LSI 3′-ALK SpectrumOrange and Vysis LSI 5′-ALK SpectrumGreen. The 2p23 ALK region in its native state will be seen as two immediately adjacent or fused (overlapping) orange/green (yellow) signals. If a chromosome rearrangement has occurred, one orange and one green signal separated by at least two signal diameters will be seen. While no ALK gene rearrangement was identified in this lesion, an ALK gene amplification (orange signal) was detected.

On imaging studies, IMTs of bone commonly demonstrate poorly delineated osteolytic lesions, without a sclerotic rim or periosteal reaction. Cortical bone destruction with extension into surrounding soft tissue may also be seen, thus giving rise to the appearance of an aggressive malignant neoplasm [3,5]. On MRI, IMTs are mostly isointense on T1-weighted images, while hypointense on T2-weighted studies [17].

IMT is a genetically heterogeneous disease, thus it is not surprising to expect varied clinical courses. IMT in children and young adults reportedly harbor clonal cytogenetic rearrangements characterized by a chromosome 2p23 that fuses to the C-terminal kinase region of the ALK gene with various partner genes, in 50–70% of cases, including TPM3, TPM4, CLTC, RANBP2 and ATIC, among a growing list of partners (Table 1). Notably, a number of ALK gene fusions have been identified in both anaplastic large-cell lymphoma (ALCL) and IMT, including ATIC-ALK and CLTC-ALK [21]. The resultant ALK rearrangement leads to activation and overexpression of the ALK C-terminal kinase regions, rendering the immunohistochemical detection of the ALK C-terminus the most efficient modality for diagnostic confirmation in practice. However, IMT with an ALK rearrangement may be rarely negative for ALK protein expression by immunohistochemistry, suggesting a non-functional/non-productive rearrangement. In questionable cases, FISH analysis using a break-apart probe may be of help. Conversely, IMT negative for an ALK gene rearrangement may rarely express the ALK protein [14]. Recent studies have suggested that this observation is due to ALKATI, a mechanism of ALK activation through an alternative transcription site [22,23]. FISH and next-generation sequencing analyses are negative in these cases, however, a large increase of ALK RNA is seen. The current case provides a potential novel molecular mechanism for the pathogenesis of IMT. The amplification of the ALK gene leads to aberrant protein overexpression, thus giving the same end result as most ALK gene rearrangements in IMT.

On the contrary, IMT diagnosed in adults older than 40 years rarely demonstrate cytogenetic alterations [24,25]. Moreover, rearrangements of receptor tyrosine kinase genes other than ALK, such as ROS1, NTRK3, PDGFRβ and Ret, have also been observed [14–16], suggesting a diverse pathogenesis for IMT. Moreover, there may be morphologic overlap between IMT and IgG4-related disease, thus emphasizing the importance of a multiplex fusion assay in the distinction of the latter from IMT [26].

Similar to other anatomical sites, surgical resection is the most common treatment modality for IMT of bone, producing the greatest number of patients with disease-free survival. However, resection often is not feasible because of tumor location and/or multifocality. These tumors typically are resistant to radiotherapy and conventional chemotherapy. The ALK inhibitor, crizotinib, has been used in patients with unresectable/multifocal ALK + IMT, with a favorable response [27]. Multiple pulmonary metastases one year after surgical resection of the affected bone was seen in one patient [4]. In general, histologic

Table 1
Summary of cytogenetic abnormalities of IMT.

Cytogenetics	Author/year	Location	No. of cases	Histomorphology	Key IHC
Rearrangements involving ALK*					
TPM3-ALK	Lawrence/2000 [25]	Abdomen, Lung	2	Plump spindle cells	ALK +
	Milne/2006 [33]	Ileum	1	Spindle cells	ALK +
	Hornick/2015 [34]		1		
	Mansfield/2016 [35]	Thigh	1		ALK +
	Bennett/2017 [36]	Uterus	1	Spindle cells	ALK +
	Lovly/2014 [15]	Mesentery, nasopharynx	4		ALK + /-
TPM4-ALK	Lawrence/2000 [25]	Abdomen	1	Plump spindle cells	ALK +
	Lovly/2014 [15]	Mesentery	2		ALK +
CLTC-ALK	Bridge/2001 [37]	Neck, pelvis	2	Spindle cells	ALK +
	Patel/2007 [38]	Retroperitoneum, abdomen	2		
	Hornick/2015 [34]		1		
	Lovly/2014 [15]	Lung, bladder, mesentery	7		ALK +
RANBP2-ALK	Ma/2003 [39]	Abdomen, mesentery, omentum	2	Spindle, stellate, epithelioid cells	ALK +
	Patel/2007 [38]	Retroperitoneal abdominal mass	1		
	Chen/2008 [40]	Liver	1	Round cell	ALK +
	Hornick/2015 [34]		4		
	Li/2013 [28]	Mesentery	2	Ganglion-like	ALK +
	Lovly/2014 [15]	Omentum	1		ALK +
ATIC-ALK	Debiec-Rychter/2003 [41]	Bladder	1	Spindle cells	ALK +
	Tateishi/2016 [42]	Mandible	1	Spindle cells	ALK +
CARS-ALK	Debelenko/2003 [30]		1		ALK +
PPFIBP1-ALK	Takeuchi/2011 [31]	Lung	1	Spindle cells	ALK +
DCTN1-ALK	Wang/2012 [43]	Neck	1	Spindle cells	ALK +
	Subbiah/2015 [44]	Uterus	1	Spindle cells	
	Taylor/2019 [26]	Lung	1	Dense lymphoplasmacytic infiltrate, storiform fibrosis,	ALK +
EML4-ALK	Sokai/2014 [45]	Lung	1	Spindle cells	–
	Muscarella/2017 [46]	Hypopharynx	1	Spindle-to-epithelioid cells	ALK +
	Lovly/2014 [15]	Lung	2		ALK + /-
	Antonescu/2015 [14]	Lung, soft tissue, omentum, trachea	7	Spindle cells, plump spindle cells, rhabdoid cells	ALK + /-
FN1-ALK	Lovly/2014 [15]	Bladder	2		ALK +
	Ouchi/2015 [47]	Bladder	1	Spindle cells	ALK +
	Hornick/2015 [34]		1		
	Haimes/2017 [48]	Uterine	2	Spindle cells	ALK +
LMNA-ALK	Lovly/2014 [15]	Mesentery	1		ALK +
SEC31A-ALK	Lovly/2014 [15]	Lung	1		ALK +
TFG-ALK	Lovly/2014 [15]	Pelvis	1		ALK +
	Taylor/2019 [26]	Trachea	1	Subtle storiform fibrosis, dense lymphoplasmacytic infiltrate	ALK +
PRKAR1A-ALK	Lovly/2014 [15]	Shoulder	1		ALK +
TIMP3-ALK	Haimes/2017 [48]	Uterus	1	Spindle cells	ALK +
	Bennett/2017 [36]	Uterus	1	Spindle cells	ALK +
IGFBP5-ALK	Haimes/2017 [48]	Uterus	3	Spindle cells	ALK +
	Bennett/2017 [36]	Uterus	2	Spindle cells	ALK +
THBS1-ALK	Haimes/2017 [48]	Uterus	3	Spindle cells	ALK +
	Bennett/2017 [36]	Uterus	3	Spindle cells	
	Taylor/2019 [26]	Pharynx	1	Marked fibrosis with subtle storiform fibrosis, dense lymphoplasmacytic infiltrate	ALK +
DES-ALK	Bennett/2017 [36]	Uterus	2	Spindle cells	ALK-
SEC31-ALK	Bennett/2017 [36]	Uterus	1	Spindle cells	ALK +
A2M-ALK	Tanaka/2017 [49]	Lung	2	Spindle cells	ALK +
HNRNPA1-ALK	Inamura/2017 [50]	Bladder	1	Spindle cells	ALK +
NUMA1-ALK	Rao/2018 [27]	Mediastinum, hemithorax, lung, pleura, liver, kidney, bone, soft tissue	1	Spindle cells	ALK +
ALK amplification	Current case	Bone	1	Spindle cells	ALK +
Rearrangements involving ROS1					
YWHAE-ROS1	Lovly/2014 [15]	Buttock, pelvis	2		
	Hornick/2015 [34]	Buttock	1	Spindle cells	
TFG-ROS1	Lovly/2014 [15]	Mesentery, Lung	2		
	Hornick/2015 [34]	Mesentery	1	Spindle and polygonal cells	
	Antonescu/2015 [14]	Esophagus, pelvis	2	Spindle cells, fascicles	ROS1 +
	Taylor/2019 [26]	Lung	1	Storiform fibrosis, obliterative phlebitis, dense lymphoplasmacytic infiltrate	ALK-/ROS-
?-ROS1	Antonescu/2015 [14]	Lung, abdomen	4	Spindle cells, fascicles, plump ovoid cells	ROS1 + /-

(*continued on next page*)

Table 1 (*continued*)

Cytogenetics	Author/year	Location	No. of cases	Histomorphology	Key IHC
Other cytogenetic alterations					
ETV6-NTRK3	Alassiri/2016 [16]	Lung, liver	2	Spindle cells	
	Takahashi/2018 [51]	Uterus	1	Spindle cells	
	Taylor/2019 [26]	Lung	1	Storiform fibrosis, obliterative phlebitis, dense lymphoplasmacytic infiltrate	ALK-/ROS-
NAB2-PDGFRβ	Lovly/2014 [15]	Peritoneum	2		
Ret rearrangement	Antonescu/2015 [14]	Lung	1	Spindle cells, 'herring-bone' fascicles	ALK +

* only listed those with known fusion partners; IHC, immunohistochemistry.

features do not correlate well with clinical behavior, with the exception of an epithelioid/round cell morphology which pursues an aggressive course with rapid local recurrence and frequent distant metastases [28,29]. RANBP2-ALK fusion and ALK-negative IMTs reportedly have a higher likelihood of metastasis in limited case series [1,29,30]. However, more highly sensitive immunohistochemical methods may be needed for an accurate diagnosis and to identify those patients who might benefit from ALK-inhibitor therapies [31]. Thus, the reliability of proposed prognostic indicators requires further validation.

In summary, we have presented a case of an IMT of bone with *ALK* gene amplification, thus resulting in overexpression of the protein. To our knowledge, this is the first reported IMT harboring a clonal *ALK* amplification in the English language literature. Given that ALK amplification has been reported in other translocation-associated tumors such as non-small cell carcinoma [32], whether these amplifications are pathogenic by themselves or they are part of a large rearrangement remains to be elucidated. Molecular genetic testing and next-generation sequencing may further expand our knowledge in the pathogenesis and discover potential novel therapeutic targets in the pursuit of precision medicine.

Compliance with Ethical Standards

The study was waived by the Institutional Review Board at the authors' institution.

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