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Case Report
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Endogenous Chondroma of the Rib: A Case Report and Gene Detection

*Liyuan Cui[#], Xin Li[#], Ming Dong, Minghui Liu, Qingchun Zhao, Hongyu Liu and Jun Chen**

Department of Lung Cancer Surgery, Tianjin Medical University General Hospital, China

[#]These authors contributed equally in this work

Abstract

Enchondroma is a benign tumor that often arises from short tubular bone and cartilage of the joints of the arms and legs, but rarely arises from the ribs. Herein, we described a 17-year-old Chinese female who presented with a 2.5 cm × 1.5 cm × 1cm mass in the left fifth rib. After resection of the lesion, a histopathologic diagnosis of endogenous chondroma was rendered. She has shown no local recurrence or distal disease in a 2 year follow-up period. Furthermore, gene detection analysis indicated that there were seven genes of BRCA1, BCL2L11, MET, NOTCH4, WT1, CCND1 and FGF19 with abnormalities, including mutation, deletion and amplification.

Keywords: Endogenous chondroma of the rib; High-throughput sequencing; Gene mutation

Introduction

Enchondroma is a relatively rare benign tumor that often arises from short tubular bone and cartilage of the joints of the arms and legs, specifically at the metaphysis, but rarely arises from the ribs. Enchondroma presents a risk of malignant transformation into chondrosarcomas, especially in Ollier disease which is characterized by widespread enchondromas with a unilateral predominance in early childhood. The therapy of enchondroma is limited, so far, surgical excision is the mainstay of treatment. Due to its rarity literature focusing on genes analysis of this disease, herein, we do genetic testing for this rare endogenous chondroma occurrences in ribs and found some genes abnormalities.

Patient Presentation

A 17-year-old female was admitted with left rib tumor that was found by the physical examinations 2 months ago. She denies fever and chest pain, and no special clinical symptoms were found. The patient had no family history of cancer and refused the same history in her relatives. A review of her systems was unremarkable. The laboratory results of a peripheral blood count, baseline serum chemistry screening, and urinalysis were normal on admission, and the tumor biomarker test also shows a negative result. The negative results of PDD and T-SPOT test help us to exclude the infection of mycobacterium tuberculosis. A Computed Tomography (CT) scan of her chest showed a clear-edged mass nearly 25 mm × 15 mm × 10 mm glowing to the abdominal in the fifth rib with the density of calcification (Figure 1A). Three -dimensional reconstruction of ribs showed a bone destruction at the left fifth rib (Figure 1B). The bone ECT scan only indicated a relatively concentrated distribution region of the left 5th anterior costal. Head and abdomen CT were not seen obvious abnormalities. An accurate diagnosis can't be given early, because it is difficult to distinguish enchondroma with fibrous dysplasia through computed tomography.

In 2016, Left chest wall mass resection with the assistance of tubeless VATS (Video-Assisted Thoracic Surgery) was performed. The front part of the 5th rib with tumor was first dissected and cut off in a bloc resection. As shown in Figure 2, the pathology diagnosis was endogenous chondroma with growing active chondrocytes and mildly shaped cells. After operation the patient recovered uneventfully and was followed up for 18-month with disease progression free, as shown in Figure 3.

Furthermore, in order to explore the molecular structure of this tumor, the mutations of 295 tumor-related driver genes are detected by a high-throughput sequencing test (Guangzhou Burning Rock Biotechnology Inc. China). All 295 genes are described as previously report (Complementary Table 1). We use the patient blood DNA as basic line to analyze the tumor tissue, after ruling out genetic variations, 5 tumor-related somatic mutations are confirmed, of which 3 genes (MET,

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Correspondence:
Jun Chen, Department of Lung Cancer Surgery, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Anshan Road No.154, Heping District, Tianjin 300052, China,
E-mail: huntercj2004@yahoo.com

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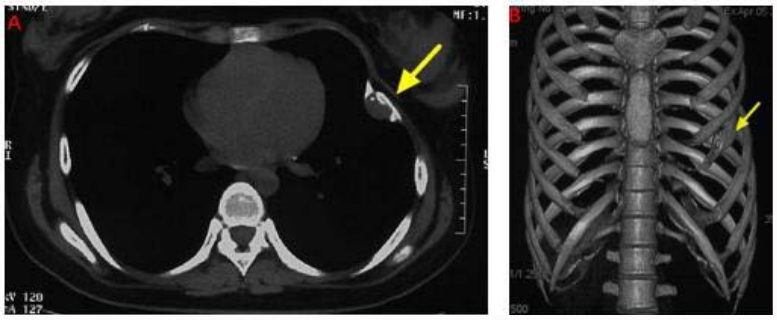

Figure 1: Computed tomography scans of chest. (A) A mass of 25 mm × 15 mm grew within the left fifth rib with the clear border; (B) A bone destruction occurred in the front of the left fifth rib, which seemed like a benign lesion.

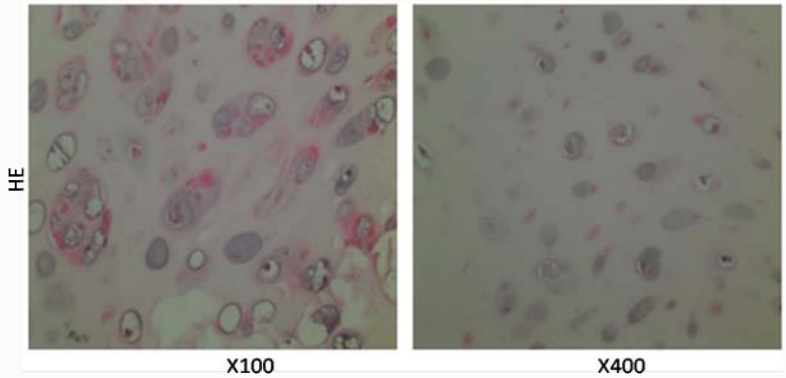

Figure 2: Pathological characteristics demonstrated by H&E staining. The pathology showed the chondrocytes are growing actively and cells are mildly atypical.

NOTCH4, WT1) were missense mutations and 2 genes of BRCA1 and BCL2L11 were deletion mutations. In additional, the amplifications of two genes (CCND1 and FGF19) were detected, as the primary database for these mutation genes are shown in Table 1.

Discussion

Endogenous chondroma is a more common benign bone tumor, divided into endogenous chondroma and sub-periosteal chondroma. It is the most common in the former [1], and the majority of this disease occurs in foot short tubular bone [2]. Endogenous chondroma are present in more than 12% of benign bone tumors, and account for 3% ~ 10% in all patients suffering bone tumors [3]. They are composed of cells derived from chondrocytes and occur as solitary lesions or multiple lesions in enchondromatosis syndromes especially in adolescent patients. Clinical symptom caused by enchondromas includes pain, skeleton deformity, even the pathological fractures [4]. Some research reveals that although it is extremely rare, there is a potential for enchondromas to have a malignant progression towards chondrosarcoma. In young Asian females the probability was reported greater than 50% in some cases of multiple enchondromatosis, such as Ollier disease or Maffucci syndrome [5]. Regular physical assessment and radiological imaging can result in earlier detection of malignant transformation.

The gene mutation researches of chondrosarcomas are limited, and the most of them focus on the Isocitrate Dehydrogenase genes (IDH1 and IDH2), which are present in the majority of chondrosarcomas. But how these mutations cause enchondromas is unclear. It is reported the mutation of IDH1 and IDH2 may produce D-2HG which can inhibit the differentiation of chondrocytes, and promote the formation of chondroma [6]. Besides of IDH, EXT was found related to the inheritance of osteochondroma, and the independent mechanisms caused by EXT1 are involved in the occurrence of these tumors [7,8].

So far, there is the lack of gene study on endogenous chondroma, especially from rib. As shown in Table 1, our study revealed 7 genes with appearing abnormalities by NGS. The gene of CCND1 located at 11q13.3 has a gene amplification (CN=4.55), It is reported in a clinical study that CCND1 protein expression was weakly positive in only 1 of 10 normal cartilage tissues and the rest were negative, whereas the positive rates of CCND1 expression in enchondromas and chondrosarcomas were 27.8% (5/18) and 60.9% (28/46) in enchondromas and chondrosarcomas, the positive expression rate was significantly higher than normal cartilage tissue, the increased expression of CCND1 protein may be related to the proliferation and differentiation of enchondromas and chondrosarcomas cells, leading to the occurrence of tumors [9]. However, the study of targeted treatment indicates that the tumor cell may be sensitive to CDK inhibitors like Palbociclib (PD-0332991) [10]. FGF19 is another amplification gene at chromosome 11 (CN=3.75), and indicates the tumor may be susceptible to FGFR inhibitors [11], like BGJ398 which is an effective FGFR inhibitor that inhibits FGFR1, FGFR2, FGFR3 and FGFR4. MET gene has a missense mutation, the basic groups G have transformed into A at the position 1933, and the amino acid changes from Gly to Arg, but there is still no evidence to prove whether the MET inhibitor works in these cases. The missense mutation of Notch 4 gene is in the exon of chromosome 6 (c.813_815del GGG) with the 272th amino acid changing from Asp to Gly. Some relative researches have revealed that the notch signaling pathway may participate in cellular differentiation and proliferation in chondrosarcoma. And the finding also indicates notch as the

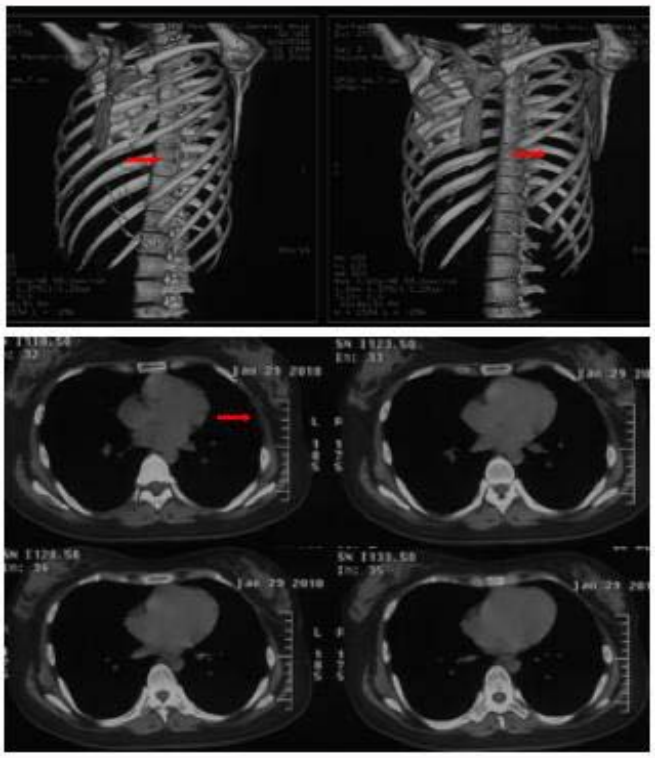

Figure 3: Computed tomography scans of chest after operation for 18-month.Upper panel showed a partial missing in the front of the left fifth rib (red arrows); lower panels also showed the missing of the left fifth rib (red arrow).

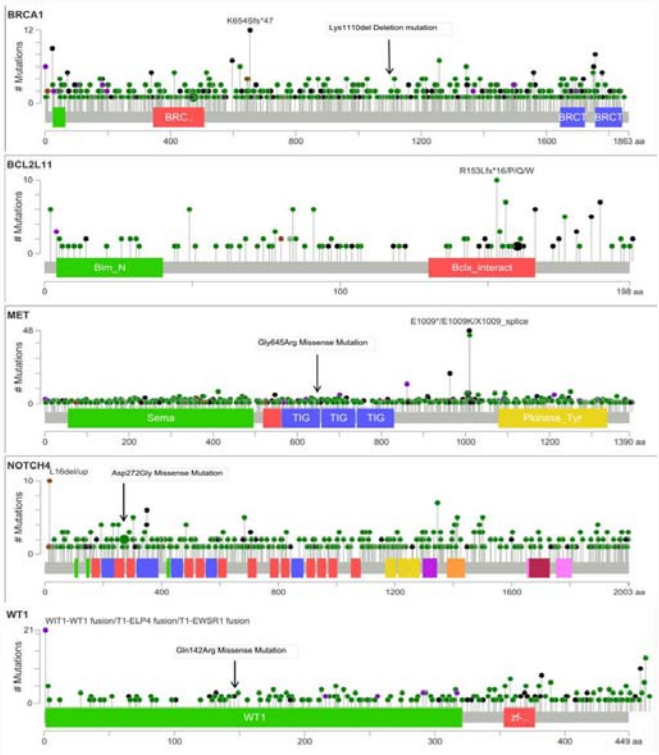

Figure 4: Gene mutation analysis results and TCGA data. The mutations of BRCA1, BCL2L11, MET, NOTCH4 and WT1 detected in this sample overlaid as black arrows on the mutation distribution diagrams of these genes from the TCGA project.

key molecules to influence the maturation of cells of chondrogenic lineage [13]. Maybe the notch gene mutation is bound up with the tumor progression of enchondroma. The Missense Mutation of WT1 in chromosome 11 make the base A become base G, therefore the change of protein comes behind. So far no targeted drug has been proved available to tumors with NOTCH4 or WT1 mutation. The

Table 1: The abnormalities of 7 genes in patient.

Gene name	chr:posi	ref.alt	frequency	Mutation type	Amino acid Change	Targeted drug
CCND1			CN=4.55	Amplification	_	Palbociclib (May sensitive)
				Position		Abemaciclib (May sensitive)
FGF19			CN=3.75	Amplification	_	BGJ398 (May sensitive)
				Position		
BRCA1	17:41199639-41199641	AGG >-	15.80%	Deletion mutation	Lys1110del	Olaparib (May sensitive)
						Veliparib (May sensitive)
BCL2L11	2:111883716	C >-	26.70%	Deletion mutation	none	Erlotinib (May resistant)
						Gefitinib (May resistant)
						Icotinib (May resistant)
MET	7:162674325	G >A	14.40%	Missense Mutation	Gly645Arg	Crizotinib (still uncertain)
NOTCH4	6:32163433- 32163435	GGG >-	24.70%	Missense Mutation	Asp272Gly	none
WT1	11:32409747	A>G	11.20%	Missense Mutation	Gln142Arg	none

Complementary Table1: Cancer-related295-gene panel.

ABL1	BRAF	CHEK2	ETV4	FGFR4	JAK2	PAK3	PALB2	RAD51D	STAG2
AKT1	BRCA1	CHUK	ETV5	FLT1	JAK3	PAK7	PARP1	RAD52	STAT4
AKT2	BRCA2	CIC	ETV6	FLT3	JUN	MRE11A	PARP2	RAD54L	STK11
AKT3	BRIP1	CRBN	EWSR1	FLT4	KDM5A	MSH2	PARP3	RAF1	SUFU
ALK	BTG1	CREBBP	EZH2	FOXL2	KDM5C	MSH6	PARP4	RARA	SYK
ALOX12B	BTK	CRKL	FAM123B	GATA1	KDM6A	MTOR	PAX5	RB1	TBX3
APC	C11ORF30	CRLF2	FAM46C	GATA2	KDR	MUTYH	PBRM1	REL	TET2
APCDD1	C17ORF39	CSF1R	FANCA	GATA3	KEAP1	MYC	PDGFRA	RET	TGFBR2
AR	CARD11	CTCF	FANCC	GNA11	KIT	MYCL1	PDGFRB	RICTOR	TIPARP
ARAF	CASP8	CTNNA1	FANCD2	GNA13	KLHL6	MYCN	PDK1	RNF43	TMPRSS2
ARFRP1	CBFB	CTNNB1	FANCE	GNAQ	KRAS	MYD88	PIK3C2G	RPA1	TNFAIP3
ARID1A	CBL	CUL4A	FANCF	GNAS	LMO1	MYST3	PIK3C3	RPTOR	TNFRSF14
ARID2	CCND1	CUL4B	FANCG	GPR124	LRP1B	NBN	PIK3CA	ROS1	TOP1
ASXL1	CCND2	CYP17A1	FANCI	GRIN2A	MAP2K1	NCOR1	PIK3CG	RUNX1	TP53
ATM	CCND3	DAXX	FANCL	GSK3B	MAP2K2	NF1	PIK3R1	RUNX1T1	TRRAP
ATR	CCNE1	DDR2	FANCM	HGF	MAP2K4	NF2	PIK3R2	SETD2	TSC1
ATRX	CD79A	DIS3	FAT3	HLA-A	MAP3K1	NFE2L2	PMS2	SF3B1	TSC2
AURKA	CD79B	DNMT3A	FBXW7	HRAS	MAP3K13	NFKBIA	PNRC1	SH2B3	TSHR
AURKB	CDC73	DOT1L	FGF10	IDH1	MCL1	NKX2-1	PPP2R1A	SMAD2	VHL
AXL	CDH1	EGFR	FGF12	IDH2	MDM2	NOTCH1	PRDM1	SMAD4	WISP3
BACH1	CDK12	EP300	FGF13	IGF1	MDM4	NOTCH2	PRKAR1A	SMARCA4	WT1
BAP1	CDK4	EPHA3	FGF19	IGF1R	MED12	NOTCH3	PRKDC	SMARCB1	XPO1
BARD1	CDK6	EPHA5	FGF23	IGF2	MEF2B	NOTCH4	PRSS8	SMARCD1	XRCC3
BCL2	CDK8	EPHB1	FGF3	IKBKE	MEN1	NPM1	PTCH1	SMO	ZNF217
BCL2L2	CDKN1B	ERBB2	FGF4	IKZF1	MET	NRAS	PTEN	SOCS1	ZNF703
BCL6	CDKN2A	ERBB3	FGF6	IL7R	MITF	NSD1	PTPN11	SOX10	
BCOR	CDKN2B	ERBB4	FGF7	INHBA	MLH1	NTRK1	RAD50	SOX2	
BCORL1	CDKN2C	ERG	FGFR1	IRF4	MLL	NTRK2	RAD51	SPEN	
BCR	CEBPA	ESR1	FGFR2	IRS2	MLL2	NTRK3	RAD51B	SPOP	
BLM	CHEK1	ETV1	FGFR3	JAK1	MPL	NUP93	RAD51C	SRC	

BRCA1 and BCL2L11 are both tested to have a deletion mutation; the former is Non-displaced deletion mutations (c.3327_3329del), which arouse an amino acid variation (p.Lys1110del). Tumors carrying BRCA1 germline or somatic mutations may be sensitive to PARP inhibitors [14,15], including Olaparib and Veliparib. The mutations of later occurred in the intron, thus, no protein has been changed. To explore the biological significance of the mutations, we examined the TCGA mutation database with our sequencing data (Figure 4). These

mutations were reported in multiple cancers from TCGA database. Especial WT1, NOTCH4 and MET genes were reported having the analogous Amino acid changing in TCGA in various cancer types but with relatively low occurrence.

Conclusion

The ribs occupied with enchondroma is relevantly rare, according to recent reports, the surgical approaches are still highly praised for the purpose of relieve clinical symptoms. This uncommon case we delivered shows several gene mutations, including missense mutation, deletion mutation and amplification. We also found some targeted drugs may sensitive to those. Although the medical treatment focus on gene target is not a mainstream, the gene research and further study of enchondroma is necessary and meaningful.

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