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

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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 × 1 cm 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, BGL2L11, 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, 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 examination 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,
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
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.

<table>
<thead>
<tr>
<th>Gene name</th>
<th>chr:posi</th>
<th>ref.alt</th>
<th>frequency</th>
<th>Mutation type</th>
<th>Amino acid Change</th>
<th>Targeted drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCND1</td>
<td>17:41199639-41199641</td>
<td>AGG -&gt;</td>
<td>15.80%</td>
<td>Deletion mutation</td>
<td>Lys1110del</td>
<td>Olaparib (May sensitive)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Veliparib (May sensitive)</td>
</tr>
<tr>
<td>BCL2L11</td>
<td>2:111883716</td>
<td>C -&gt;</td>
<td>26.70%</td>
<td>Deletion mutation</td>
<td>none</td>
<td>Erlotinib (May resistant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gefitinib (May resistant)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Icotinib (May resistant)</td>
</tr>
<tr>
<td>MET</td>
<td>7:162674325</td>
<td>G &gt;A</td>
<td>14.40%</td>
<td>Missense Mutation</td>
<td>Gly654Arg</td>
<td>Crizotinib (still uncertain)</td>
</tr>
<tr>
<td>NOTCH4</td>
<td>6:32163433-32163435</td>
<td>GGG -&gt;</td>
<td>24.70%</td>
<td>Missense Mutation</td>
<td>Asp272Gly</td>
<td>none</td>
</tr>
<tr>
<td>WT1</td>
<td>11:32409749</td>
<td>A&gt;G</td>
<td>11.20%</td>
<td>Missense Mutation</td>
<td>Gln412Arg</td>
<td>none</td>
</tr>
</tbody>
</table>

**Complementary Table1**: Cancer-related295-gene panel.

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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**References**