Original Article
Benign notochordal cell tumor: a retrospective study of 11 cases with 13 vertebra bodies

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Abstract: Purpose: To analyze the clinical data, MRI, pathological diagnosis, treatment and long-term effects of benign notochordal cell tumor (BNCT), a newly described novel spine tumor. Methods: We retrospectively studied 11 patients’ clinical data of the above. Results: The ratio of males to females was 4:7, and the average age was 49.2 years (range, 18-74 years). Cervical vertebra (5; 38.5%) and thoracic vertebra (5; 38.5%) were the most frequent site followed by the lumbar vertebra (3; 23%). Pain was the main symptom except case 2 who were diagnosed accidentally because of prostate cancer. The mean delay from first clinical symptoms to diagnosis was ranged from 2 months to 20 years. MRI showed all BNCTs were osteolytic lesions with hypointense on T1-weighted sequences, hyperintense on T2-weighted sequences. There were 4 vertebral bodies with wedge fracture. There were two cases that had two noncontiguous vertebral bodies with BNCT. In histology, marrow replacement was noted by multivacuolated physaliphorous cells immunoreactive for CK, EMA and S100 protein. All 10 cases except case 2 had vertebral reconstruction and fixation with different methods. Of the 11 patients, 9 had full follow-up data which showed no evidence of recurrence or metastasis without further treatment. Conclusion: Noncontiguous multi-centricity BNCTs are rare. No specific vertebrae are more frequently involved. Once BNCT is diagnosed by pathology, the surgical intervention is necessary for the patients with obvious clinical symptoms although it is benign. There is no evidence of BNCT recurrence or metastasis.

Keywords: Benign notochordal cell tumor, bone marrow, pathology, magnetic resonance imaging

Introduction
Notochord-related tumors of the spinal column include benign notochordal cell tumor (BNCT), ecchordosis physaliphora and chordoma. The first two are generally considered benign tumors, but the last one is considered to be malignant. BNCT was described many years ago in literature and defined in 2013 WHO Classification of Tumors of Soft Tissue and Bone [1]. Till now, there is not much information available about it. Although it is similar histologically to chordoma, their clinical behavior is different, so the treatment and prognosis are not the same. There were a few published papers of BNCT case report and no large series of case study. In this paper, we reported 11 cases of spinal BNCT’s clinical data, pathological features and differential diagnosis, treatment and prognosis.

Patients and methods
We conducted a retrospective cohort study in which all patients evaluated at our hospital between 2005 and 2013 with a pathological diagnosis of notochordal lesions were identified by fine-needle aspiration or surgical resection. Eventually 11 cases were diagnosed as BNCT by more than three more experienced pathologists according to the fourth edition of the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone was published in February 2013 [1].

Data collection
All clinical data were collected from the electronic files for patients with BNCT. Follow-up data was obtained from hospital charts and, if necessary, by a phone call. For the patients we
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Imaging

All patients were examined with magnetic resonance imaging (MRI) before and X-ray after surgical treatment.

Treatment

Depending on the condition and concomitant disease, all patients received a different method of vertebral reconstruction fixation or vertebroplasty.

Results

Clinical features

There were 11 patients (13 vertebral bodies) with BNCT in our study (Table 1), with the disease more frequently in females than in males (7:4; 63.6%). The average age of patients was 49.2 years (range, 18-74 years). Cervical vertebra (5; 38.5%) and thoracic vertebra (5; 38.5%) was the most frequently involved site of BNCT, followed by the lumbar vertebra (3; 23%). Two cases each had two noncontiguous vertebral bodies with BNCT—case 3 was the T2 and T8, and case 4 was T6 and T8. Pain was the main symptom at presentation. The mean delay from first clinical symptoms to diagnosis was ranged from 2 months to 20 years. 10 patients had back pain except case 2 without symptom, who was found vertebral lesions when he had bone scan because of prostate cancer. The pathological diagnosis of the vertebra was BNCT but prostate cancer metastasis by fine needle aspiration biopsy. Case 6 had schwannoma in L2 while BNCT in L3.

Imaging findings

Two of the 4 cases performed CT showed mild sclerosis of the vertebral body without bone destruction. On MRI of the 11 cases with 13 BNCT vertebra bodies, all BNCTs were osteolytic lesions with hypointense on T1-weighted sequences, hyperintense on T2-weighted sequences, and hyperintense on short T1 inversion recovery sequences with well margin. No lesions exhibited extension past the vertebral

Table 1. Clinical characteristics of 11 patients with benign notochordal cell tumor

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Presenting Symptoms</th>
<th>Delay Time (mo)</th>
<th>Vertebral Level</th>
<th>Unrelated Problems</th>
<th>Vertebral Level</th>
<th>Treatment Method</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>18</td>
<td>L back P</td>
<td>3</td>
<td>L5</td>
<td>Spina bifida</td>
<td>L5</td>
<td>Fixation</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>74</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Prostatic cancer</td>
<td>No</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>63</td>
<td>Back P, Zonesthesia</td>
<td>39</td>
<td>T2, T8</td>
<td></td>
<td></td>
<td></td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>70</td>
<td>Back P</td>
<td>2</td>
<td>T6, T8</td>
<td></td>
<td></td>
<td>Fixation</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>50</td>
<td>Neck and shoulder p</td>
<td>3</td>
<td>C5</td>
<td>Wedge fracture</td>
<td>T8</td>
<td>Fixation</td>
<td>26</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>54</td>
<td>L back P</td>
<td>20 y</td>
<td>L3</td>
<td>Slipped disk</td>
<td>L2/3, 3/4, 4/5</td>
<td>Verteoplasty</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>53</td>
<td>L back P</td>
<td>6</td>
<td>L1</td>
<td>Schwannoma</td>
<td>L2</td>
<td>Verteoplasty</td>
<td>47</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>36</td>
<td>Chest &amp; back</td>
<td>6</td>
<td>T7</td>
<td></td>
<td></td>
<td>Fixation</td>
<td>86</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>39</td>
<td>Neck P</td>
<td>3</td>
<td>C5</td>
<td>Wedge fracture</td>
<td>T7</td>
<td>Verteoplasty</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>24</td>
<td>Neck P</td>
<td>2</td>
<td>C2</td>
<td>Wedge fracture</td>
<td>C2</td>
<td>Fixation</td>
<td>47</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>62</td>
<td>Neck and shoulder p</td>
<td>5</td>
<td>C6</td>
<td>Wedge fracture</td>
<td>C6</td>
<td>Fixation</td>
<td>No</td>
</tr>
</tbody>
</table>

P means pain.
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body into the paraspinal or epidural compartments. Case 6 had schwannoma in L2. Case 3 (Figure 1) and case 4 (Figure 2) each had two vertebral bodies involved. The wedge fracture in case 4, case 8, case 10, and case 11 and slipped disk in case 5 and C1 dislocation in case 10 were been diagnosed on MRI. X-ray but not MRI was used to observe the situation of the patient fixation.

Treatment choice

There was different method of treatments according to the BNCT, the concomitant diseases, the patient’s condition and other factors. All the 11 cases had fine needle aspiration biopsy before surgical treatment. Case 2 had no resection of other form therapy after fine needle aspiration biopsy diagnosed as BNCT. The other 10 patients with 12 vertebra bodies had some range curettage. No one had complete vertebrectomy. Case 1 had L5 vertebrectomy reconstruction fixation because he had spina bifida at the same L5 level. Although case 3 and case 4 both had two noncontiguous vertebral bodies involved, case 3 had bone cement injection to fix the two BNCT vertebral bodies because the two involved vertebra bodies were distance and the spine was good stability (Figure 3), while case 4 had vertebral reconstruction fixation of the two involved vertebra bodies because of the T8 wedge fracture (Figure 4). The case 5 had vertebral reconstruction fixation because the patient had multiple disc herniation and the BNCT in one of them. So discect-
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Figure 5. Paraffin-embedded tissues show the BNCT is slight yellow. Multiple dark red spots diffusely distributed in the tumor are the marrow island.

Figure 6. Photomicrograph of Figure 5 demonstrates BNCT in the part vertebral body and the multiple bone marrow islands in the tumor tissue (Hematoxylin and eosin; original magnification × 40).

Histological changes

The reason of case 7 and case 9 with vertebral reconstruction fixation was chronic pain. The case 8, case 10 and case 11 had vertebral reconstruction fixation because of the wedge fracture or with vertebra dislocation.

Figure 7. BNCT tumor cells with clear cytoplasm existing bone trabeculae. Marrow isolated island with adipocytes in it is visible. Red blood cells are diffuse or focal distribution within the tumor (Hematoxylin and eosin; original magnification × 400).

Histological changes

The specimen was broken because most patients had curettage. The gross of the lesion was slight yellow or gray with ill-defined. Some time dark red marrow spots could be seen in the tumor tissue (Figure 5).

Microscopically, the part marrow in the involved vertebral body was replaced by tumor cells with clear cytoplasm, arranged in cord- and nest-like pattern and permeated between the existing bone trabeculae with ill-define border under low power field. There were few focally bone marrow nests. Red blood cells were diffuse or focal distribution within the tumor (Figures 6, 7). Under high power field, the cells were multi-vacuolated and physisaliphorous. The nuclei were small and located in the cell edge or inside the cytoplasm. Adipocytes presented in the marrow nest within the tumor. Compared to the normal trabeculae surrounding the tumor, some trabecular distribution within the tumor was thicker with bone deposition on the trabecular surface (Figure 8). It lacked lobulation, fibrous bands, morphological heterogeneity, nuclear atypia, mitotic figures, necrosis bone destruction, myxoid stroma, syncytial cell strands, or soft tissue invasion.

Immunohistochemically, the tumor cells of all the 11 cases were diffusely positive for pancytokeratin (AE1/AE3) (Figure 9), epithelial membrane antigen (EMA), S100 and vimentin, moreover CK18, galectin-3 and HBME-1 were positive too. The tumor cells were weakly and focally positive for S100 protein in case 1 and case 4 in the T8. CD10, SMA, calponin, desmin, and GFAP were negative. The Ki-67 labeling index was approximately 1% in all.

Follow-up

There were 9 patients had effective follow-up data. Case 10 and case 11 were lost to follow-up.

All of the remaining patients were alive without further treatment except case 2 who had antiandrogen therapy. All the 9 patients had no evi-
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Figure 8. BNCT cells are multivacuolated. Some trabecular distribution within the tumor is thicker with bone deposition on the trabecular surface (Hematoxylin and eosin; original magnification × 400).

Figure 9. Immunohistochemical examination showed AE1/AE3 diffuse positive. The marrow island and the adipocyte in it were negative (× 400).

dence of recurrence or distant metastasis in imaging, with follow-up times ranging from 3 to 95 months (mean 39 months).

Discussion

The first examples of the existence of ectopic notochord remnants in an adult’s axial skeleton were described in the latter half of the 19th century by German scientists, considered at first as degenerating cartilage; it was soon postulated to represent a notochordal remnant, a view eventually confirmed by Ribbert in 1895. At the 1996 meeting of the International Skeletal Society (ISS), such benign notochordal lesion, morphologically different from chordoma and fetal notochord elements, was put forth [2]. Till now, there were some sporadic reports in the literature, with a lot of controversy [3]. This study analyzed the clinical data, diagnosis process and therapy methods of 11 BNCT cases. It may be the largest one in the several small number of cases reported.

A variety of diagnostic names have been affixed to the notochordal-type vertebral lesion, including benign chordoma, notochordal rest, giant notochordal rest, giant notochordal hamartoma, ecchordosis physaliphorous vertebraalis, benign notochordal lesion, and BNCT, all of which refer to the same morphological entity, as a matter of personal choice. In the fourth edition of the World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone was published in February 2013, BNCT was defined as a benign tumor showing notochordal differentiation [1].

The notochord, which serves as the inducer of vertebral column formation, develops during the third week of gestation [4] will become the future vertebral bodies of the mobile spine, intervertebral disc and nucleus pulposus. Then the notochord itself degenerates, breaking up into segments, become positioned within the site of the spinal column. So it not normally found in the vertebral body beyond 10 weeks of gestation [4]. However, there were some studies reported that notochord be found in infants and the age of 10 years, and even middle-aged adults [5]. In this study, case 2 was 18-year-old and case 10 was 24-year-old, the rest were in the middle-aged and aged. All patients were older than 10 years. Females were more than males while equal sex distribution was reported in the literature. The average age of patients was consistent with the literature [6].

The majority BNCT was small lesions that are generally incidentally found because of other diseases or autopsy, but larger BNCTs may be incidentally with back pain. A different degree of back pain was the main or only symptom of BNCT or without pain throughout body [3]. In our study, all patients had pain except case 2 who was found vertebral lesions when he had bone scan because of prostate cancer. Symptom duration was various from several months to several years. Noted in our 11 patients, case 3 was more than 3 years, cases 11 was more than 20 years and the other limited within 2 months to 6 months.

Till now, there was no a study showing that which BNCT most likely occurs in vertebral
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body. Most cases had single vertebral body involved. McCarthy [7] and Yamaguchi et al. [8] had reported that noncontiguous multi-centricity BNCTs were rare. In our study, case 3 and case 4 had two noncontiguous vertebral body involved. All the four vertebral bodies were diagnosed as BNCT by pathology.

The Roentgenographic results of BNCT were usually normal or osteolytic defects [6]. Fracture or some sclerosis was been diagnosed. CT showed no apparent vertebral abnormality or demonstrated some degree of vertebral body sclerosis without any bone destruction. Magnetic resonance imaging (MRI) studies in all demonstrated a lesion within and confined to the vertebral body. Data on the lesions’ T1/T2 signal intensity strength was usually low T1-/high T2-weighted images [1].

Histologically, the lesion consisted of a solid, sheet-like proliferation of univacuolated and physaliphorous cells that were permeated between the existing bone trabeculae lacked lobulation, fibrous bands, morphological heterogeneity, nuclear atypia, bone destruction, myxoidstroma, syncytial cell strands, or soft tissue invasion, all of which are characteristic features of chordoma. The tumor cells were immunoreactive for pancytokeratin (AE1/AE3), epithelial membrane antigen (EMA), vimentin and S100 protein [9]. Immunostains cannot be used to distinguish GNR from chordoma although brachyury, galectin-3 and HBME-1 [9-11] and CK18 [12-14] had been reported. In our study, galectin-3, HBME-1 and CK18 was positive.

In histology, there were several diseases required to be distinguished from BNCT, such as chordoma and giant notochordal rest [12]. It also must be differentiated with other diseases, such as metastatic cancer with vacuoles cells, vertebral adipose tissue metaplasia, and the bone diseases with vacuoles cells. Entrapped intralesional marrow could present in some cases [14]. There was no reported that there was red blood cells diffusely or locally distributed within the tumor. But, we could not sure it was a tumor phenomenon or artifact.

Imunohistochemical staining can help in the differential diagnosis of these diseases. Although metastatic cancer with vacuoles cells was positive for AE1/AE3, EMA and even vimen-

Since BNCT was benign and non-progressive, it has been stated that they may not require operative intervention unless radiological evidence indicating malignant transformation [8, 15]. However, this was not universally true, as some patients may have debilitating chronic pain attributable to the lesion or the involved vertebral body fracture, and require surgical operation or vertebral resection for relief or fixation [16, 17]. That was to say, treatment should be decided according to the specific circumstances of the patients. The therapy method was different with range from curettage to complete vertebrectomy and then vertebral reconstruction fixation. In our study, all the patients had fine needle aspiration biopsy and diagnosed as BNCT by pathology. Case 2 had no resection and other therapy after fine needle aspiration biopsy. Case 1, case 5 and case 6 had vertebral reconstruction fixation because they had other diseases in the BNCT vertebral body. The case 8, case 10 and case 11 had vertebral reconstruction fixation because of the wedge fracture or with vertebra dislocation. Case 3 and case 4 had vertebral reconstruction fixation because there two vertebral bodies involved which caused the instability. The reason of case 7 and case 9 was chronic pain. Case 3 had bone cement injection into the two BNCT vertebral bodies.

Till now, there was some controversy about the relationship of BNCT and chordoma. There were reports about coexisted BNCT and chordoma. BNCT is a precursor lesion to chordoma or chordoma can be said to arise from the benign-appearing notochordal tissue, which is still a controversial issue [18, 19]. In this study, we had no evidence about the relationship of BNCT and chordoma. Maybe we need more cases with sufficient long-term follow-up to evaluate the ultimate fate of these lesions.

In summary, we present the largest series of cases of spinal BNCT with clinical and pathological analysis. Patients have a widely-distributed age range. Two noncontiguous multi-centricity BNCTs are rare. No specific vertebrae are
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more commonly involved. It is important to make correct pathological diagnosis and differential diagnosis to further treatment. Although BNCT is benign and non-progressive, it is necessary to take operative intervention when patients have obvious clinical symptoms or secondary diseases. Treatment should be taken according to patients’ specific conditions. There is no evidence of BNCT recurrence or metastasis.

Disclosure of conflict of interest

None.

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