Clinicopathological Characteristics of Chordoma: An Institutional Experience and a Review of the Literature

Kordomunun Klinikopatolojik Özellikleri: Bir Kurum Deneyimi ve Literatür Derlemesi

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OZ

AMAC: Tek bir kuruluşdan kordomaların klinikopatolojik özelliklerini incelemek.

YONTEM VE GERECLER: Bu çalışma, 2006 ile 2010 yılları arasındaki 5 yıllık bir dönemde Srinagar’daki Sher-i-Kashmir Tip Bilimleri Enstitüsünde tanı konmuş 18 kordoma olgusunun retrospektif bir analizidir.


SONUÇ: İlk olarak agresif, kordomalar etkin bir şekilde tedavide edilebilir.

ANAHTAR SÖZÜKLER: Kordoma, Clivus, Sakrum, Kondroid kordoma, Dediferansiyeli kordoma

INTRODUCTION

Chordoma is a rare, primary bone tumor arising from primitive notochord remnants of the axial skeleton. It accounts for 1-4% of all primary skeletal tumors (15, 8). The sacrum represents the most common anatomical site of origin accounting for 50-60% of all cases followed by the skull base region (25-35%), the cervical vertebrae (10%) and the thoracolumbar vertebrae (5%). Chordomas show a dual epithelial and mesenchymal differentiation (19). Histopathologically, chordomas may show a ‘typical/classical’ morphology, a ‘chondroid’ morphology showing large islands of hyaline cartilage with areas showing classical morphology and a ‘dedifferentiated’ morphology showing sarcomatous areas interspersed with areas of classical chordoma (24). The biological behavior of chordomas is characterized by a generally slow aggressive local growth with a low to late tendency in metastasizing to distant sites including the lung, bone, soft tissue, lymph nodes, liver and skin (19). Up to 40-60% of patients develop distant metastases over the course of their disease (14). Surgery remains the cornerstone of chordoma treatment (11). Complete radical resection is however difficult because by the time the symptoms appear the tumor is so large that complete excision is frequently impossible (18). Thus despite its low-grade malignancy, chordoma has a low long-term local control rate.
The importance of radiation therapy, however, has increased over time in the treatment of local recurrent disease. We hereby analyze 18 cases of chordoma and discuss their clinicopathological characteristics and their outcome.

PATIENTS and METHODS
A retrospective analysis of all the cases of chordoma diagnosed in the department of Pathology at Sher-i-Kashmir Institute of Medical Sciences from January 2006 to December 2011 was done. This institute is a 650-bed tertiary care hospital in Kashmir which caters to the entire population of Kashmir valley, India. The clinical details of the patients were abstracted from the case records and relevant slides and blocks of the cases were retrieved and reviewed by a single pathologist. Fresh slides and sections were cut and wherever needed, special stains, i.e. PAS (periodic acid Schiff) with/without diastase, were used. Immunohistochemistry (IHC) was used for confirmation of diagnosis.

RESULTS
Demographic and Clinical Profile
The overall mean age of the patients was 46.72 years (range 14-60 years). Females presented at a younger mean age (40.25 years) than males (48.57 years). Male: female ratio was 14:4. The commonest symptom was low back pain, it was seen in all patients with lumbosacral chordomas (n=15). Radiculopathy was noticed in 5/18 (27.77%) patients, constipation in 4/18 (22.22%) and urinary symptoms in 2/18 (11%). Other symptoms seen were diplopia (11%), palpable swelling (11%) and quadripareisis (5.5%) (Table I). The average duration of symptoms was 11.8 weeks (range 2-24 weeks). There was no gender difference in the duration of symptoms (p>0.05).

Imaging
MRI was available in all the cases and CT scan in 16 cases. Calcification on CT scan was noted in 50% cases. MRI showed most of the lesions to be hypointense on T1- and hyperintense on T2-weighted sequences. Preoperative impression of chordoma was made on imaging in most of the cases however, in few patients other possibilities viz. metastasis, chondrosarcoma, schwannoma and lymphoma were also thought of. Imaging revealed involvement of sacrum in 61% (11/18), sacrococcygeal region in 11% (2/18), clivus in 11% (2/18), lumbosacral region in 5.5% (1/18), lumbar spine in 5.5% (1/18) and upper cervical region in 5.5% (1/18) of patients (Figure 1A-C).

Surgery
All the patients underwent surgery. Total excision of the tumor along with resection of the lower sacrum (S3 and below) was possible in 6 patients as there was no involvement of S2 or above. Other 9 patients of sacral chordomas were subjected to subtotal excision of the tumor because of widespread involvement of the surrounding tissues by the tumor. Two patients of clival chordoma underwent presigmoid subtemporal approach and subtotal excision of the tumor. One patient of C1-C3 tumor was managed by trans-oral decompression of the tumor with 2nd stage occipito-cervical contour rod fixation.

Histopathological/Cytological Characteristics
Fine needle aspiration cytology was done in 2 patients of sacral chordomas preoperatively who had palpable tumor masses and in both cases abundant mucinous matrix with physalipharous cells were seen and a diagnosis of chordoma was suggested which was later confirmed on histopathology. Crush biopsy was done in 16 cases of chordoma, of which the diagnosis of chordoma was given in 15 cases. In one case of clival chordoma, the material was non-crushable. The histopathology in most cases showed classical morphology of chordoma.

Figure 1: Imaging shows sacrococcygeal chordoma (A), chordoma involving the craniovertebral junction (B) and post-tumor resection CT scan of the sacrum and pelvis (C).
Table I: Demographic and Clinical Profile of Patients

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/ gender</th>
<th>Site of lesion</th>
<th>Symptomatology</th>
<th>Histopathology</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40/M</td>
<td>Clivus</td>
<td>Diplopia (2 weeks)</td>
<td>Chondroid chordoma</td>
<td>EBRT 20 cycles RT, 6 years on follow up</td>
</tr>
<tr>
<td>2</td>
<td>40/M</td>
<td>C1–C3</td>
<td>Spastic quadriaparesis (2 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 6 years on follow up</td>
</tr>
<tr>
<td>3</td>
<td>35/M</td>
<td>Sacral</td>
<td>Low back ache, radiculopathy, constipation (2 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 5 years on follow up</td>
</tr>
<tr>
<td>4</td>
<td>42/M</td>
<td>Sacral</td>
<td>Low back ache, urinary retention (1 month)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 3 years on follow up</td>
</tr>
<tr>
<td>5</td>
<td>37/F</td>
<td>Clivus</td>
<td>Diplopia (3 weeks)</td>
<td>Chondroid chordoma</td>
<td>No follow up</td>
</tr>
<tr>
<td>6</td>
<td>50/F</td>
<td>Sacral</td>
<td>Low back ache, radiculopathy (4 months)</td>
<td>Chondroid chordoma</td>
<td>EBRT 20 cycles RT, 2 years on follow up</td>
</tr>
<tr>
<td>7</td>
<td>50/M</td>
<td>Sacral</td>
<td>Painful visible swelling over sacral area, constipation (3 months)</td>
<td>Conventional Chordoma (FNAC done)</td>
<td>EBRT 20 cycles RT, 2 years on follow up</td>
</tr>
<tr>
<td>8</td>
<td>45/M</td>
<td>Sacral</td>
<td>Low back ache (5 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 2 years on follow up</td>
</tr>
<tr>
<td>9</td>
<td>50/M</td>
<td>Sacral</td>
<td>Low back ache, pain (4 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 2 years on follow up</td>
</tr>
<tr>
<td>10</td>
<td>60/M</td>
<td>Lumbar</td>
<td>Low back ache (5 months), spastic paraplegia, retention of urine (1 week)</td>
<td>De-differentiated chordoma with metastasis to cervical vertebrae</td>
<td>Died within 3 months</td>
</tr>
<tr>
<td>11</td>
<td>45/M</td>
<td>Sacral</td>
<td>Low back ache (6 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 2 years on follow up</td>
</tr>
<tr>
<td>12</td>
<td>45/M</td>
<td>Sacrococcygeal</td>
<td>Difficulty in walking, pain lower back, radiculopathy (3 months)</td>
<td>Chondroid chordoma</td>
<td>EBRT 20 cycles RT, 2 years on follow up</td>
</tr>
<tr>
<td>13</td>
<td>53/M</td>
<td>Sacral</td>
<td>Low back ache (2 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 1 year on follow up</td>
</tr>
<tr>
<td>14</td>
<td>55/M</td>
<td>Sacral</td>
<td>Low back ache (3 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 1 years on follow up</td>
</tr>
<tr>
<td>15</td>
<td>60/F</td>
<td>Sacral</td>
<td>Low back ache (4 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 1 year on follow up</td>
</tr>
<tr>
<td>16</td>
<td>60/M</td>
<td>Sacrococcygeal</td>
<td>Constipation, low back ache (1 month)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 3 years on follow up. Recurred in 2011 re-operated and subjected to RT.</td>
</tr>
<tr>
<td>17</td>
<td>14/F</td>
<td>Sacral</td>
<td>Constipation, difficulty in walking, pain (1 month), palpable swelling (1 week)</td>
<td>Conventional Chordoma (FNAC done)</td>
<td>EBRT 20 cycles RT, 1 year on follow up</td>
</tr>
<tr>
<td>18</td>
<td>60/M</td>
<td>Lumbosacral</td>
<td>Low back ache, difficulty in walking (6 months)</td>
<td>Conventional Chordoma</td>
<td>EBRT 20 cycles RT, 6 months on follow up</td>
</tr>
</tbody>
</table>

Age in years. **EBRT**- external beam radiotherapy; **RT**- Radiotherapy; **M**- male, **F**- female.
Chordoma is a relatively slow-growing invasive neoplasm that destroys and replaces the bone in which it develops and sometimes causes distant metastasis. It develops from the embryonic remnants of the notochord which undergo neoplastic transformation and develops most commonly in the axial skeleton at the base of the skull and sacrococcygeal region, infrequently in other vertebrae and rarely extra-notochordally.

Because of the rarity of this tumor, there are only a few published series on chordoma. This tumor usually occurs in the middle-aged population. The median age has been reported to vary from 59-62 years (1,11). In our series these tumors occurred at a relatively younger age than reported in the literature (26). We had a median age of 46.72 years in our patients. The tumor has a predilection for males (1,11,26). We observed a 7:2 ratio in favor of males. Although sex is not thought to be of prognostic value in chordomas, it has been suggested that female sex is an independent predictor of shortened survival in skull base chordomas (20). We in our series did not notice such a finding.

The duration of symptoms before diagnosis is long with a median duration of 12 months (4,10) but the duration of symptoms was relatively short, i.e., 11.8 weeks (range 2-24 weeks) in our study. The sacrum is the commonest site hence duration of low back ache before the patients present to the physician is long compared to when the clivus is involved which may present with diplopia because of involvement of the abducent nerve and alerts the patient early. This was obvious in our series also where the tumors involving the clivus presented within one week while sacral chordomas reported within 1-6 months.

Pain was the predominant symptom in our series. In a study on 27 patients with sacral chordoma in a 40 year period, all but one of the patients presented with back pain and lower extremity pain and seventeen patients presented with autonomic dysfunction as evidenced by sphincter or sexual dysfunction (26).

**DISCUSSION**

Chordoma is a relatively slow-growing invasive neoplasm that destroys and replaces the bone in which it develops and sometimes causes distant metastasis. It develops from the embryonic remnants of the notochord which undergo neoplastic transformation and develops most commonly in the axial skeleton at the base of the skull and sacrococcygeal region, infrequently in other vertebrae and rarely extra-notochordally.

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CT scan reveals a midline sacral lytic lesion. Calcification is seen in 50-70% tumors. Often there is a large presacral mass. MRI reveals the mass to be hypo and hyperintense on T1- and T2- weighted sequences respectively. Isotope scan shows a normal or decreased uptake. The extent of the tumor is best seen on MRI scan. On imaging the differential diagnosis includes other primary bone tumors, metastasis, multiple myeloma and lymphoma. All the metastatic lesions on MRI will be hypointense on T1-weighted and hyperintense on T2-weighted sequence. Sacral chordomas and chondrosarcomas have specks of calcifications. Multiple myeloma involving the bone shares the same characteristics on MRI imaging. MRI is better in delineating the soft tissue involvement and CT is sensitive in documenting whether the lesion is lytic or sclerotic and also in detecting the calcifications (17). We noticed calcification in 50% cases and MRI showed the classical hypo- and hyperintensity of the lesions on T1- and T2-weighted sequences respectively. Isotope scan was not done in any of our patients.

In a large study of spinal chordomas, 48% involved the sacrococcygeal region, 38.5% occurred at the skull base and the remainder along the mobile spine (5). In a series of 25 patients with chordoma the site of origin of chordoma was the sacrum in 11 patients, spine in 13 patients and skull base in one patient (11). In the Danish national study, based on the data of 37 patients in 25 years, the tumors were located in the sacrococcygeal region in 68%, sphenoid-occipital region in 16% and vertebrae in 16% (1). In our study, the majority (72%) tumors were located in the sacrococcygeal region, 11% in the clivus, 5% in upper cervical region, 5% in the lumbar region and 5% in the lumbosacral region.

The primary modality of treatment in chordomas is surgery. The extent of resection is dictated by the site of the lesion (23). Tumors involving the sacrum below S-2 without involvement of sacroiliac joint can be managed by total resection of the tumor without any compromise of the major neurological functions. If total sacrectomy is done for high sacral tumors, instrumentation and fusion is needed to provide mechanical support to spine (13). Tumors of the clivus are best managed by subtotal decompression and radiotherapy. These present a major challenge to the neurosurgeon because gross total removal of the tumor with preservation of neural and vascular structures is difficult (20). High cervical tumors can be managed by trans-oral decompression and posterior stabilization of the spine (2).

The extent of initial surgical resection plays an important role in the subsequent surgical outcome of sacral chordomas. Complete and radical resection contributes to high local control rate and the prolongation of disease-free survival (26). Looking at the resectability of sacral chordomas, most series have reported difficulty in obtaining wide surgical margins and the expected local failure rate in case of a marginal resection is in excess of 70% (13,21). Local recurrence is closely related to surgical margins (16,22,26). York JE et al reported that local control rates were 60-80% in cases who

**Figure 3:** Kaplan–Meier survival analysis shows the effects of gender (A), site of tumor (B) and histopathology (C). There was no correlation between survival and gender or site of tumor. There was a trend of correlation between survival and histopathological subtype which however was not statistically significant.
underwent total excision as compared with rates of 25-50% in subtotal resection and demonstrated a statistically significant difference in the time from surgery to local recurrence between patients who underwent radical resection and those who underwent subtotal resection (26). The primary modality of treatment in our patients was surgery. Total excision of the tumor along with the resection of the lower sacrum and coccyx was done in 6 patients in whom we obtained wide surgical margins. Of the other nine patients with sacral chordoma in whom subtotal resection was done with postoperative radiotherapy, only one of our patients had recurrence after two years.

Beigh P et al (3) reported inadequate surgical margin to be an independent prognostic factor for tumor-related death. Although intrallesional resection is not a preferred treatment option because of the worse control of tumor and the higher relative risk of reduced survival associated with this procedure, the anatomic characteristics of tumor location and spreading not infrequently result in patients having unresectable tumors or tumors that can only be incompletely resected. Intensive radical resections have been associated with greater neurological deficits (25). Total sacrectomy may sometimes warrant a colostomy or a permanent urinary diversion (9). In our patients with chordomas involving the sacrum above the level of S1S2, partial removal of the tumor with postoperative radiotherapy was highly effective. The surgery was not staged as has been done in some series (11).

Surgery with postoperative radiotherapy was very effective in our patients and following points are worthy of note:

1. None of our patients had wound dehiscence or postoperative wound infection.
2. None of our patients required a colostomy or a permanent catheter.
3. With surgical intervention, the symptoms of pain, urinary dysfunction and bowel dysfunction improved considerably.
4. All our patients were ambulatory and showed improvement in the neurological deficits after surgery.
5. The surgery in all patients was performed as a single-stage procedure.
6. The outcome was good even in patients in whom the wide resection margins were not obtained and were subjected to postoperative radiotherapy after subtotal resection.

We recommend that adequate surgery with wide margins should be performed in centers having technical expertise. The extension of margins believed to be a very important prognostic factor and being correlated with the incidence of local relapses and overall survival in many series (7) did not alter prognosis considerably in our series.

REFERENCES


