Clinicopathological patterns of osteosarcoma in Sudanese patients

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Abstract

Osteosarcoma is a high-grade malignant mesenchymal tumour capable of forming lace-like bony matrix. It has a bimodal incidence distribution, with the highest peak in the second decade and a lesser peak in late adult life.

Materials and Methods

This is a retrospective descriptive hospital-study, which took place in three central Khartoum-Sudan laboratories. Files, X-rays films and/or reports and hematoxylin and eosin (H&E) stained slides of diagnosed 50 osteosarcoma patients have been retrieved from the archives (2006 to 2011) and analyzed using Statistical Package for the Social Sciences (SPSS) program.

Results

Fifty-eight percent of patients were males and 42% were females. Twenty-two percent of patients live in Khartoum state, while 56% live in district states. Living in Khartoum conferred early detection and shorter duration of symptoms. The mean duration of symptom was 7 months. Pain and swelling comprised the cardinal presenting features. Four patients presented with pathological fractures. Metaphysis of long bones was the forerunner hotspot comprising 74%, of whom, 60% were around the knee joint. Sixty-four percent of cases originated in the medulla and 12% from the cortex.

Conventional osteosarcoma represents 72% of cases with predominance of the osteoblastic
type. Eighty percent of cases were assigned as high grade.

**Conclusion**
The most common affected age group with osteosarcoma was teenagers. Patients residing in Khartoum seek medical advice earlier; often with less advanced disease than remote areas residents. The majority of tumors were of high grade.

**Keywords:** osteosarcoma, osteoblastic osteosarcoma, fibroblastic osteosarcoma, chondroblastic osteosarcoma, periosteal osteosarcoma, parosteal osteosarcoma telangiectatic osteosarcoma, juxtacortical, medullary, and metaphysis.

**Introduction**
Osteosarcoma is a high-grade malignant mesenchymal tumor, of osteogenic origin, which is capable of forming lace-like bony matrix. It usually afflicts teenagers during the rapid growth spurt. A lesser peak has been recognized during late adult life, often with preceding pathological entities such as Paget’s disease of bone or previous radiotherapy. An association of osteosarcoma with rare familial cancer syndromes (e.g. Li Fraumeni, Retinoblastoma, and Rothmund-Thomson syndrome) which may result in polyostotic tumors, often in a younger age than the mean.

The World Health Organization (WHO) classifies osteosarcoma into medullary and cortical variants, both with low grade and high grade entities, along with other special types that have a specific histomorphological defining features.

Diagnosis of osteosarcoma is usually warranted by plain X-ray, CAT scan and an MRI scan (superior in detecting soft tissue extension of the tumor). The fine needle aspiration of the lesion is hampered by the difficult accessibility to early lesions with intact, often sclerotic cortex. The standard histopathological specimen confirms the diagnosis, classifies and grades the lesion, paving the way towards tailored treatment modalities. A second post-neoadjuvant specimen is attained to assess the residual tumor burden (percentage of tumor necrosis), which predicts the prognosis. Within the era of novel diagnostic and treatment techniques, few markers retain solidity among others, and may reserve a sound role in practice (isocitrate dehydrogenase 1 (IDH1), P53, lactate dehydrogenase LDH).

**Material and Methods**
This is a descriptive hospital based-study spanning the duration from 2006 to 2010. The study took place in three central-Khartoum laboratories. Decalcified paraffin-embedded surgical specimens (slides and blocks), along with X-ray films or reports were retrieved from the archives. Patients diagnosed with osteosarcoma during the study period and who had available archived files and slides (or blocks) were included in the study (64 cases). We had excluded 14 cases, which, either did not satisfy inclusion criteria, having poor quality slide or paraffin block specimen, or had an inconclusive evidence of malignancy based on the slide morphology alone and lacking the consolidating radiographic X-ray films or reports.

**Growth and pattern analysis**
The Tumors were classified according to the growth patterns on conventional H&E stained slides, which has been blindly double-checked by the researchers. Tumors growth behavior depicted on the slides were classified according to the WHO-International Agency for Research on Cancer (IARC) classification system of bone tumors and graded with a four-tier system according to the guidelines of Broder’s (adopted by Mayo Clinic).

The collected data was analyzed using the SPSS-14 developed by IBM company, and was tabulated and schematically presented in charts and figures.

**Results**
Of the 64 cases evaluated, 14 were excluded. The minimum age was 2 years, and the
maximum age was 63 years. The mean age was 17 years (Fig 1).

Fig 1: The age distribution of osteosarcoma patients in our study (in years)-(n=50).

Fifty-eight percent of patients were males and 42% were females. Twenty-two percent of patients live in Khartoum state, while 56% live in district states (Table 1).

Table 1: Geographic locales of patients presented with osteosarcoma in the studied group (n=50).

<table>
<thead>
<tr>
<th>Geographic locales</th>
<th>Frequency</th>
<th>Percent%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khartoum</td>
<td>11</td>
<td>22%</td>
</tr>
<tr>
<td>North</td>
<td>10</td>
<td>20%</td>
</tr>
<tr>
<td>East</td>
<td>4</td>
<td>8%</td>
</tr>
<tr>
<td>West</td>
<td>6</td>
<td>12%</td>
</tr>
<tr>
<td>Central</td>
<td>8</td>
<td>16%</td>
</tr>
<tr>
<td>Not specified</td>
<td>11</td>
<td>22%</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>100%</td>
</tr>
</tbody>
</table>

The mean duration of symptoms prior to presentation and attaining the biopsy was 7.3 months and ranged from 2 to 24 months. Sixty-eight percent of the patients presented within 3-8 months (n=9 in 3-5 months and n=5 within 6-8 months). Only 4% was presented within 3 months. Sixteen percent was presented within 9-11 months. More than one year duration of symptoms was recorded in 18% of the subjects.

Pain and swelling comprised the cardinal presenting features. Four patients presented with pathological fractures (Table 2).

Table 2: Presenting symptoms among osteosarcoma patients in studied group (n=50).

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>Swelling</th>
<th>Pain</th>
<th>Fracture</th>
<th>Metastasis</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>14</td>
<td>0</td>
<td>92</td>
<td>84</td>
<td>76</td>
</tr>
<tr>
<td>Yes</td>
<td>86</td>
<td>100</td>
<td>8</td>
<td>8</td>
<td>22</td>
</tr>
</tbody>
</table>

Metaphysis of long bones was the forerunner hotspot comprising 74%, of which, sixty percent were around the knee joint. Sixty-four percent of cases originated in the medulla and 12% from the cortex.

Twenty-two subjects presented with right sided lesions, while 20 subjects presented with left sided lesions. The skeletal hotspots of osteosarcoma in our study are depicted in Fig 2.

Fig 2: Anatomical sites involved by osteosarcoma in the studied group (n=50).
Seventy-six percent (n=38) of osteosarcoma aroused within the metaphyseal part of the bone. Diaphyseal location was recorded in 2% of the patients (n=1). Osteosarcomas arising from flat bones represented 12%. Compartment localization was not specified in 10% of patients (n=5). Medullary versus cortical tumors origin ratio was 5.3:1 (n=31/6). Conventional osteosarcoma comprised 72% of the tumors (osteoblastic 44%, fibroblastic 22% and chondroblastic 22%) (Fig 3).

**Fig 3:** Conventional osteosarcoma. Curetting specimen, osteoblastic type from distal femur in a 39-year-old male, this tumor exhibits osteoid matrix predominance.

Telangiectatic variant was recognized in 4% of the patients (n=2). Juxta-cortical tumors comprised 12% (4% periosteal and 8% parosteal). Other variants were recognized as follows: 4% small cell osteosarcoma, 6% giant cell rich osteosarcoma and 2% low grade central osteosarcoma.

**Discussion**

The slight male (1.2:1) predominance coincides with SEER program (1975-1995) published data (1.16:1)\(^\text{17}\). Participants age in our study, ranged from 2 to 63 years. The median age for presentation is 17.5 year, the mode is 13 and the SD is 17. The majority of patients were teenagers (56%). Only one recorded case was < 2 year and only 2 cases strayed beyond 50 years limit. Osteosarcoma is vanishingly rare in subjects < 5 years. Charlis PJ et al recorded an osteosarcoma in a 26 months old child involving proximal humerus\(^\text{18}\). A recurrent parosteal osteosarcoma in a 2 years old child involving the talus bone was recorded by Charlis PJ et al\(^\text{19}\).

Comparable data denote that the peak incidence of bone cancer (19 per million) occurred at age 15 according to United States SEER Program (1975-1995)\(^\text{17}\). Pubertal delay or late presentation might explain this apparent slight age shift.

Twenty-two percent of patients lived in Khartoum state (n=11) while 56% lived in other states (n=28); the residence was not specified in 22% of cases (n=11). No cases from southern Sudan have been reported, whether this is a genuine scarcity or a referral bias, it remains to be elucidated.

Living in Khartoum conferred early detection and shorter duration of symptoms (55% present <6 months) compared to remote residencies (32% present <6 month) prior to obtaining the biopsy and diagnosis (p= <0.05). Transportation obstacles, seasonal traffic blockage, security issues and not least financial reasons could be the culprit factors.

Pain and swelling constituted the constant presenting symptoms (100% and 86% of cases respectively). Eight percent (n=4) of cases were presented with pathological fractures, which is statistically associated with the telangiectatic type (p= <0.05). Published data revealed that telangiectatic osteosarcoma presents with pathological fractures in one third of cases. We have reported 2 cases of telangiectatic variant in our series, both presented with pathological fractures, our hypotheses is that the late presentation attributed to the constant accompanied fractures\(^\text{20-25}\). Bjorn et al states that symptomatic pain occurs in 85% of cases, this may be due to their early cases detection\(^\text{26}\). Pain is experienced early and may be intensified at night. The roomy copious
metaphyseal medullary bone provides a large potential space for tumor extension. The pain may last several weeks without noticeable swelling. As the tumor expands the medulla it extends through the cortex towards the neighbouring soft tissues. The pain is intensified soon as the highly innervated periosteum is preached, with the sequential classic X-ray evidences (sunray cortical appearance and Codman triangle). Juxtacortical osteosarcomas extend directly to adjacent soft tissue. Twenty-two percent of cases (n=11) presented with other symptoms (loss of weight, constitutional symptoms and symptoms related to biological extension of the tumor other than metastasis). Metastatic deposits were presented in 8% (n=4) of cases, the lung represented the solely site of these reported metastasis in our study. Pulmonary metastasis from osteosarcoma occurs in 30% to 40% of cases according to FA Schutz et al. Whether our remarkably lower figure is a genuine peculiar biologic behavior or represented a tip of an iceberg of a larger group escaped under the scrutiny, the later hypothesis is more likely the cause, adding the tendency to present lately in a significant group of our patients.

The case with 2 years duration of symptoms is a parosteal osteosarcoma, which has been diagnosed previously as osteochondromas, with a subsequent resurgence of symptoms and a popliteal fossa mass, which, is a classic site of this variant. The mode was 4 months. Sixty-eight percent of patients lapsed between 3 to 8 months before presentation and 18% presented 1 year after emergence of symptoms, either as a recurrent tumor or an indolent low grade tumor (example; parosteal osteosarcoma). Results of scientific data presented by Sneppen O et al revealed a delay of about 6.4 months. The duration of symptoms combined the period prior to presentation and doctor delay time. The later comprised the time elapsed since presentation till final disclosure of diagnosis (9 weeks according to Björn et al). Doctor’s delay time including the laboratory TAT (turnaround time) is not elucidated in our data. Biopsy techniques analysis revealed the practitioners preference of incisional technique, which, is an invasive and an irritating method, that might triggers distant metastases deposits and contaminates the surgical fields. Curetting facilitates tumours dissemination, notably when used for an erroneously presumed indolent tumor nature (e.g. aneurysmal bone cyst versus telangiectatic osteosarcoma). Such approaches should be discouraged, while a core needle biopsy technique should be encouraged.

In our study, osteosarcoma occurred predominantly in the metaphysis of long bones; representing 74% (n=37) (60% of cases aroused around the knee joint), only one case (2%) occupied the mid shaft of long bone (diaphysis; femur). Six percent of cases (n=3) aroused within flat bone (craniofacial, jaw and vertebra); one case (2%) was incited in extra-skeletal location. Locations were not specified in 10% of cases (n=5), Campanacci et al depicted similar results. Sixty-two percent (n=31) of cases aroused within the medullary part, in contrast to 12% (n=6) which aroused from the cortical part, in 24% of patients the original site were not specified (n=12). One case aroused from an extra-skeletal site; the mammary gland of a female in her fifth decade of life. Total body skeletal survey to exclude bone primaries was performed. Skeletal hot spots of osteosarcoma (60% around the knee joint) were statistically correlated with teen age incidence (p=<0.05). These figures matched international figures (WHO). The incidences of the different variants of osteosarcoma in our study coincide with WHO indices. Seventy percent of cases were G3 (35 patients) and 20% (10 patients) were G2; while only 10% of cases were G4.
Telangiectatic osteosarcoma and small cell osteosarcoma were assigned as G4. The telangiectatic variant recognized by some experts as G3, and the observed higher incidence of metastases is attributed to the mistreatment it often received, due to false impression of indolent mimickers such as aneurysmal bone cyst\(^{(29)}\). These above mentioned figures coincided with the CAP pragmatic approach of grading osteosarcomas. The predominance of the conventional type (72%) matched the peak of G3. The smaller G2 and G4 shouldering peaks represented the more indolent low grade central and parosteal osteosarcomas and the aggressive small cell and telangiectatic variants of osteosarcoma respectively. Mitotic figures were counted per 10 (X40) HPF using Olympus microscopes CX31\(^{®}\) with a 0.65mm field diameter, a range with a minimum of 1 figure and a maximum of 50 figures/10HPF were recorded among cases, 12 figures represented the mode and the median. Two-thirds of cases had > 10 figures/10 HPF (26% of them are \(\geq\) 20/10 HPF) and 44% < 10 figures/10 HPF. These values coincided with published data\(^{(7)}\).

In conclusion, the median age at presentation of osteosarcoma was 17 years. Living in Khartoum, conferred earlier in the detection of osteosarcoma and shorter duration of symptoms. Almost all osteosarcoma patients are presented with pain and swelling around the knee bony ends, which are the most frequent site of osteosarcoma. Pathological fracture is a constant presenting symptom of telangiectatic variant of osteosarcoma. Osteosarcomas preferably metastasize to the lung. Osteoblastic variant outnumbered the fibroblastic and chondroblastic variants of osteosarcoma, almost doubling comparable WHO indices.

**Recommendation**

1. Adopting standardized decalcification techniques for received specimens.
2. Standard protocols for dispatching the specimens properly and urgently to the nearby laboratory.
3. Revising the current management protocols and conducting short and long terms survival studies.
4. Evaluating the values of molecular ancillary techniques in promoting management and survival.

**References**


