Proximal femoral osteosarcoma: Diagnostic challenges translate into delayed and inappropriate management

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ABSTRACT

Background: The proximal femur is an uncommon site of osteosarcoma. The unusual manifestations at this site may lead to diagnostic and therapeutic mistakes. We therefore performed a retrospective study to estimate the proportions of patients with imaging study findings and/or clinical manifestations typical for osteosarcoma and/or inappropriate treatment decisions.

Hypothesis: Proximal femoral osteosarcoma often produces atypical clinical and radiological presentations.

Material and methods: Consecutive patients who underwent surgery at our center to treat proximal femoral osteosarcoma were included. For each patient, we collected the epidemiological characteristics, clinical symptoms, imaging study findings, treatment, and tumor outcome. Proportions were computed with their confidence intervals.

Results: Twelve patients had surgery for proximal femoral osteosarcoma between 1986 and 2015. Imaging findings were typical in 1 (8%) patient; they consisted of ill-defined osteolysis in 11/12 (92%) patients, a periosteal reaction in 1/12 (8%) patient, soft tissue involvement in 7/12 (58%) patients, and immature osteoid matrix in 11/12 (92%) patients. No patient had the typical combination of pain with a soft tissue swelling. Management was inappropriate in 2/12 (17%) patients, who did not undergo all the recommended imaging studies before surgery and were treated in another center before the correct diagnosis was established. At last follow-up, 4 patients had died (after a mean of 7 years) and 8 were alive (after a mean of 4 years).

Conclusion: Proximal femoral osteosarcoma is uncommon and rarely produces the typical clinical and imaging study findings. The atypical presentation often results in diagnostic errors and inappropriate treatments. Ill-defined osteolysis on standard radiographs should prompt computed tomography or magnetic resonance imaging of the proximal femur. Treatment in a specialized center is imperative.

Level of evidence: IV, retrospective study.

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1. Introduction

Osteosarcoma is the most common malignant bone tumor, with an incidence twice that of chondrosarcoma [1]. The main sites of involvement are the metaphyses of the distal femur (40%), proximal tibia (16%), and proximal humerus (15%) [2]. Osteosarcoma of the proximal femur accounts for fewer than 5% of cases [1,3]. Diagnostic challenges may therefore arise, in particular due to the high incidence of trauma and metastatic disease at this site.

Age at diagnosis of osteosarcoma ranges from 10 to 30 years [2]. The typical presentation combines pain with a mixed inflammatory and mechanical time pattern and a swelling over the lesion.

However, a pathological fracture may be the inaugural manifestation. Osteosarcomas at unusual sites often produce less typical manifestations, resulting in diagnostic difficulties and delays. Another risk is inappropriate management, which has a major adverse impact on the functional outcome and may diminish patient survival [4]. The proximal femur is a highly unusual site. Thus, proximal femoral osteosarcoma is at high risk for diagnostic delay and inappropriate management.

To our knowledge, no published studies have specifically assessed the clinical and radiological features of proximal femoral osteosarcoma or the consequences of inappropriate management. We therefore performed a retrospective study to estimate the proportions of patients with imaging study findings and/or clinical manifestations typical for osteosarcoma and/or inappropriate treatment decisions. We also assessed tumor outcomes. The working hypothesis was that proximal femoral osteosarcoma often produces atypical clinical and radiological presentations.

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2. Material and methods

2.1. Patients

A retrospective descriptive single-center study was performed at a bone malignancy referral center. Patients treated surgically at the study center for proximal femoral osteosarcoma between 1986 and 2015 were identified. The inclusion criterion was osteosarcoma confirmed by a review of the pathology slides at the study center and located at the proximal femur (defined as predominantly involving the femur proximal to the lesser trochanter). We excluded patients who did not undergo first-line or revision surgery for the osteosarcoma (e.g., those seen only for a second opinion). Standard resection and reconstruction techniques were applied, as described extensively elsewhere [5]. We identified 12 patients, 8 males and 4 females aged 14 to 64 years (mean, 36 years).

2.2. Methods

For each patient, we reviewed the radiographs and Computed Tomography (CT) scans to record the following: osteolysis with the appearance of the contours (well-defined by a sclerotic rim, well-defined with no sclerotic rim, or ill-defined) (Figs. 1 and 2), a periosteal reaction (no periosteal apposition or sunburst pattern with Codman’s triangle and/or apposition), cortical disruption, and/or spread to the adjacent soft tissues. Preoperative Magnetic Resonance Imaging (MRI) scans of the entire femur (Fig. 3) were reviewed for spread to the joint (abnormal synovial membrane enhancement after gadolinium injection) and skip metastases in the femur at a distance from the primary tumor. Remote metastases were sought by reviewing the CT of the chest and technetium-99 bone scintigraphy.

We also collected the following data for each patient: age, gender, circumstances of the diagnosis (symptoms, pathological fracture, incidental), time from symptom onset to treatment initiation, symptoms (pain; limp, joint stiffness, and other joint symptoms; decline in general health; swelling), and physical findings (soft tissue mass, joint motion restriction). All pathology slides were reviewed by pathologists specialized in primary bone malignancies.

Information was sought on the type of surgery performed in each patient and on the use of chemotherapy before and/or after surgery. Recurrences, metastases, and survival were recorded.

2.3. Assessment methods

The primary evaluation criterion was the proportion of patients with typical imaging study findings defined as presence of the four following findings on at least one of the preoperative imaging studies (radiograph, CT, MRI): ill-defined osteolysis, periosteal reaction, soft tissue spread, and immature osteoid bone matrix (cloud-like opacity). The secondary evaluation criteria were the proportion of patients with a typical clinical presentation, the proportion of patients who received inappropriate treatment, and the long-term tumor outcome. A typical clinical presentation was defined as a combination of pain with a mixed inflammatory and mechanical time pattern, joint symptoms, and a soft tissue mass. Appropriate management was defined as the following sequence, in the order indicated: physical examination; appropriate imaging studies including a radiograph, CT scan of the proximal femur, and MRI of the proximal femur; discussion of the case during a multidisciplinary meeting, biopsy collection complying with standards for musculoskeletal tumor biopsies [6–8], another multidisciplinary discussion, and appropriate oncological and surgical treatment. The long-term tumor outcome, last known status of the patient (disease-free or alive with disease), local recurrences, and metastases were recorded.

2.4. Statistical methods

No sample size estimation was performed, since consecutive patients were enrolled. Continuous data are described as median (interquartile range) and categorical data as number (%). The point-estimate of the percentage with its Confidence Interval (CI) is reported for each evaluation criterion [9]. Long-term tumor outcome was assessed based on Kaplan-Meier survival estimates. Statistical analyses were performed using R software version 3.2.2.

Fig. 1. Standard antero-posterior radiograph of the right hip: osteosarcoma of the proximal femur.

Fig. 2. Computed tomography, axial section: osteosarcoma of the proximal femur.
Fig. 3. Magnetic resonance imaging of a proximal femoral osteosarcoma. (a) Coronal T2-weighted view showing a high-signal lesion with post-gadolinium enhancement; (b) Coronal T1-weighted view: low signal intensity from the lesion; (c) axial T2-weighted view showing a high-signal lesion with post-gadolinium enhancement; (d) axial T1-weighted view: low signal intensity from the lesion.


3. Results

A single patient (1/12, 8%) had typical imaging study findings (Table 1). Ill-defined osteolysis was seen in 11/12 (92%) patients, a periosteal reaction in 1/12 (8%) patient, soft tissue spread in 7/12 (58%) patients, and immature osteoid bone matrix in 11/12 (92%) patients. Spread to the joint was noted in 3/12 (25%) patients. No skip metastases were found.

No patient had the typical combination of pain with a soft tissue swelling. Symptoms were the main presentation: thus, 11/12 (92%) patients presented with pain and a limp. None of the patients had a palpable soft tissue mass (Table 2).

Management was inappropriate in 2/12 (17%) patients. These 2 patients did not undergo all the recommended imaging studies before surgery. They underwent total hip arthroplasty at another center for incorrect diagnoses of suspected avascular necrosis of the femoral head and non-pathological femoral neck fracture, respectively. The remaining 10 patients received the entire appropriate management sequence.

Neoadjuvant chemotherapy was given to 11/12 (92%) patients and postoperative chemotherapy to 11/12 (92%) patients. Surgery was performed in 11/12 (92%) patients. Among them, 10/11 (83%) patients underwent extensive tumor resection, which was intra-articular in 9/10 (90%) patients and extra-articular in 1/10 (10%) patient. The remaining patient (1/11, 9%) required hip disarticulation.

Table 1
Radiological findings in the study patients; the data are n (%).

<table>
<thead>
<tr>
<th>Osteolysis</th>
<th>Radiography</th>
<th>CT</th>
<th>MRI</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-defined, sclerotic rim</td>
<td>1 (8)</td>
<td>1</td>
<td>1</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Well-defined, no sclerotic rim</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ill-defined</td>
<td>11 (92)</td>
<td>9</td>
<td>11</td>
<td>11 (92)</td>
</tr>
<tr>
<td>Periosteal reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>12 (100)</td>
<td>9</td>
<td>11</td>
<td>11 (92)</td>
</tr>
<tr>
<td>Aggressive</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Spread to soft tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (8)</td>
<td>1</td>
<td>7</td>
<td>7 (58)</td>
</tr>
<tr>
<td>No</td>
<td>11 (92)</td>
<td>9</td>
<td>5</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Spread to hip joint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3 (25)</td>
</tr>
<tr>
<td>No</td>
<td>12 (100)</td>
<td>10</td>
<td>9</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Osteoid bone matrix</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (92)</td>
<td>10</td>
<td>11</td>
<td>11 (92)</td>
</tr>
<tr>
<td>No</td>
<td>1 (8)</td>
<td>0</td>
<td>1</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

CT: Computed Tomography; MRI: Magnetic Resonance Imaging.
Table 2
Main epidemiological and clinical features of the study patients.

| Demographics |  
|--------------|-----------------|
| Age, years\(^a\) | 31.5 (18–52.5) |
| Females/Males, n (%) | 4 (33)/8 (66) |
| Circumstances of diagnosis, n (%) |  
| Symptoms | 11 (92) |
| Pathological fracture | 2 (17) |
| Incidental | 10 (83) |
| Symptoms, n (%) |  
| Pain | 11 (92) |
| Restricted joint motion range | 1 (8) |
| Swelling | 0 |
| Decline in general health | 1 (8) |
| Time from symptom onset to treatment, months\(^a\) | 7 (5.75–9.25) |

\(^a\) median (Q1–Q3)

Survival rates were as follows: 1 year, 100% (95% CI: [100%–100%]); 2 years, 89% (95% CI: [71%–100%]); and 5 years, 89% (95% CI: [71%–100%]). At last follow-up, 4/12 (33%) patients had died of the malignancy, after a mean of 7 years; 4/12 (33%) patients were alive and free of disease, after a mean of 4 years; and 4/12 (33%) patients were alive with disease, after a mean of 4 years. During follow-up, 2/12 (17%) patients developed local recurrences and metastases after a mean of 5 years and 5/12 (42%) others had metastases without local recurrences after a mean of 6 years; of these last 5 patients, 2 died and 3 were alive at last follow-up.

Of the 2 patients who initially underwent total hip arthroplasty due to diagnostic errors, 1 experienced a local recurrence and metastases after 6 years and died 1 year later. The other had no recurrence after oncological surgery and was alive at last follow-up.

4. Discussion

Osteosarcoma arises predominantly in the metaphyses of the long limb bones, including the distal femur in 40% of cases [2]. Involvement of the proximal femur is rare, accounting for less than 5% of all osteosarcomas [10,11]. The clinical and radiological presentation of this unusual location is often atypical and may therefore fail to raise a sufficient level of clinical suspicion. The result may be a missed diagnosis and inappropriate treatment. We therefore conducted a retrospective cohort study of patients with proximal femoral osteosarcoma to characterize the features of the unusual presentation at this site.

This study has several limitations. First, the small sample size, which reflects the low incidence of proximal femoral osteosarcoma, limits the precision of our estimates of proportions of patients with typical radiological and clinical presentations. Second, the absence of a control group leaves open the possibility that the unusual features in our patients may not have been more common than at more typical sites such as the distal femur and proximal tibia. Finally, all 12-study patients were eventually managed at a referral center. Thus, selection bias may have occurred, limiting the external validity of our findings. In addition, the tumor outcomes obtained at a referral center such as ours may not apply to other centers. More specifically, the local rescue treatment performed after total hip arthroplasty involves extensive extra-articular resection followed by a specific reconstruction technique that cannot be recommended in all centers.

The typical radiological presentation of osteosarcoma combines signs of a bone malignancy, namely, ill-defined osteolyis, a periosteal sunburst reaction, and soft tissue spread; with the presence of immature osteoid bone matrix [12,13]. In our study, a single patient (1/12, 8%) met all these criteria. The main determinant of failure to consider a radiographic diagnosis of proximal femoral osteosarcoma is the absence of a periosteal reaction. None of our patients had a periosteal reaction visible on standard radiographs and only 10% had a periosteal reaction by CT. Only ill-defined osteolysis, whose interpretation may pose challenges to clinicians with limited experience, is of a nature to cause concern. Similarly, by MRI, only half the patients had evidence of soft tissue spread, a finding typical for malignant tumours. The second factor that complicates the interpretation of imaging studies of the proximal femur is possible confusion with the many other disorders that occur at this site. The osteolysis seen in avascular necrosis of the femoral head is well defined but difficult to evaluate, due to projection of the acetabulum on standard radiographs. The frequency of avascular necrosis and its possible occurrence in young patients may direct clinicians away from a detailed analysis of the radiograph and the obtaining of additional investigations that might challenge the diagnosis, and the result may then be inappropriate management by total hip arthroplasty [14]. Other lesions that commonly involve the proximal femur include benign lytic lesions such as essential bone cyst and fibrous dysplasia, as well as chondroblastoma, whose far greater frequency may therefore provide the clinician with unwarranted reassurance [15–21]. In sum, although a detailed evaluation of the full battery of imaging studies readily suggests proximal femoral osteosarcoma, thus indicating a need for a bone biopsy, the crucial decision node is placed further upstream, at the step of standard radiography, which must be painstakingly analyzed to determine that a bone malignancy might be present and, therefore, that further investigations are in order before surgery is considered.

The clinical presentation of proximal femoral osteosarcomas disconcerting due both to the unusual epidemiological features and to the absence of a soft tissue mass. In our study, half the patients were older than 40 years and had an unremarkable medical history. In contrast, in studies of osteosarcoma the proportion of patients older than 40 years is usually about 10% [2]. Furthermore, the deep location of the proximal femur within the periarticular soft tissues precludes palpation of a mass during the physical examination, whereas at the knee a swelling is very often felt.

Of our 12 patients, 2 (17%) were inappropriately managed. The clinical and radiographic presentation did not suggest a bone malignancy and the imaging studies needed to refine the analysis were not obtained. Although this proportion may seem small, the major medical and psychological consequences of missing the diagnosis of a severe malignancy must be borne in mind. A multidisciplinary discussion must take place before the bone biopsy to ensure optimal technical conditions for this procedure [7] and to avoid the devastating consequences of an inadequate biopsy [6,8]. Mistakenly performing a total hip arthroplasty results in malignant cell dissemination into the joint and surrounding soft tissues. Hip disarticulation is then required for the local rescue treatment, resulting in poorer functional outcomes than with initial appropriate surgery.

The overall 5-year survival rate in our population was 89% with a 95% CI of 71%–100%, in keeping with previously published studies showing 5-year survival rates of 70% to 80% [22–24]. On average, conservative surgery to treat long-bone osteosarcoma is followed in 4% to 10% of cases by a local recurrence after an interval of at least 30 months [24]. In our study, the local recurrence rate of 2/12 (17%) is slightly higher than for osteosarcoma at other sites. In a study of 1702 patients included in Cooperative Osteosarcoma Study Group investigations, Bielack et al. [2] found that location at the proximal femur was associated with the highest recurrence rate among all long-bone locations and that involvement of the proximal limbs carried a higher mortality rate than distal involvement [2].

5. Conclusion

Orthopedic surgeons and radiologists must be aware of the atypical clinical and radiological features of proximal femoral...
osteosarcoma. The atypical presentation at this site results in diagnostic delays and may lead to inappropriate treatments that result in a loss of chance for the patient. At the proximal femur, osteosarcoma is difficult to diagnose clinically due to the paucity of the symptoms and limited contribution of the radiographs: the main sign is ill-defined osteolysis, which may be difficult to detect. MRI should be performed at the slightest doubt to maximize the likelihood of an accurate diagnosis despite the long list of differentials. A correct diagnosis is essential, as treatment must be provided by a referral center for primary bone malignancies.

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Disclosure of interest

The authors declare that they have no competing interest.

References