Intramedullary Well-Differentiated Osteosarcoma: Imaging and Pathologic Findings in a Group of 17 Patients

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Abstract

Background: Intramedullary well-differentiated osteosarcoma (IMWDOS) is rare and may easily be misdiagnosed.

Objective: This study was to investigate the clinical, imaging and pathological features of IMWDOS for correct diagnosis.

Materials and methods: Seventeen patients with IMWDOS were enrolled and the clinical, imaging and pathological data were analyzed.

Results: There were 13 males and 4 females with an age range of 19-55 years (mean 32). The lesion was located at long bones in 16 patients and at the second region of acetabulum in one patient. Except for three patients with limited areas of lesions, all the other patients had wide areas of disease, and the lesion in long bones all involved the metaphysis area with possible extension towards the diaphysis. In imaging, the lesion usually had an unclear boundary with destruction of bone cortex, uneven thickness of the bone cortex, thick and coarse trabecula in the lesion, but few periosteal reaction and soft tissue masses. The lesion was histologically composed of spindle cells with slight atypia. Follow-up was performed 2-101 months (mean 37.7) in 14 cases, 10 years in one case and 26 years in the remaining two. At follow-up, 12 patients (12/17 or 70.6%) who had complete resection including amputation (n=2), wide excision (n=8) and endoprosthetic replacement (n=2) had no recurrence or metastasis. Among five patients with curettage, three (3/17 or 17.6%) were recurrent with two deaths, and the third one died during post-operation chemotherapy.

Conclusion: Intramedullary well-differentiated osteosarcoma tends to occur at the metaphysis of long bones especially at the distal femur involving a large area. Histological, clinical and imaging data have to be closely combined to reach the correct diagnosis.

Introduction

Osteosarcoma is a high-grade tumor usually developing in the intramedullary cavity of long bones in adolescents and young adults. Well differentiated osteosarcoma of the bone is rare and accounts for 1%-2% of all osteosarcomas with an equal gender distribution1,2. This type of bone osteosarcoma was first described by Unni et al in 19773,4, and later the World Health Organization described it as low-grade central osteosarcoma (LGCOS)5. Unlike most osteosarcomas, LGCOS is less aggressive with limited metastatic potential and a good prognosis4,6. Nonetheless, the tumor may recur locally to exhibit greater malignancy with an increased potential for metastasis7,8, and the current standard treatment modality for LGCOS is wide resection with a negative margin. Although this disease is rare, the high differentiation and low malignancy contribute to a high rate of misdiagnosis initially, presenting similarly as fibrous dysplasia, giant cell tumors, and chordrosarcoma in the clinical manifestation. The difficulty in managing patients with LGCOS lies in diagnosing the disease correctly, and the radiological appearance is often confused with that of fibrous dysplasia, desmoplastic fibroma, nonossifying fibroma, osteoblastoma and aneurysmal bone cysts1,9-13. It is consequently vital to combine both histopathological and radiological findings to reach a correct diagnosis. Our study analyzed the clinical, imaging and pathological findings of seventeen patients with intramedullary well-differentiated osteosarcoma (IMWDOS) and presented our experience in diagnosing this disease.

Materials And Methods

This study was approved by the hospital ethics committee with all the patients given their written informed consent. The data of fifteen patients with IMWDOS confirmed by histological examinations were collected between January 2000 and June 2017, and additional two patients with IMWDOS confirmed 26 years ago were also enrolled, with a total number of 17 patients ranging 19-55 (mean 32) years in age. There were 13 males and 4 females. Two patients were found to have IMWDOS because of trauma resulting in pathological fracture, and the rest 15 patients had bone pain, discomfort or restricted activity of the affected limb with aggravated symptoms at presentation. The duration of symptoms lasted for three years in one patient and 2-12 months (mean 8.2) in the rest. All patients had plain radiography, fourteen patients had preoperative computed tomography (CT) scanning, and nine patients had magnetic resonance imaging (MRI) of the affected areas. Pathological specimens in all patients were evaluated by two experienced pathologists for confirmation of the disease. All patients had post-operation follow-up, with 26 years in two patients, ten years in one and 2-101 months (mean 37.7) in the rest patients. Among sixteen patients with IMWDOS in the long bones, two patients had amputation with the limb and four patients had endoprosthetic replacement of either allograft or autograft with a follow-up duration ranging 2-80 months (mean 23), one curettage patient had 10-year follow-up, and four patients had curettage with a post-operation follow-up of 13-45 months (mean 31.3). One patient with long bone IMWDOS had internal fixation at the initial pathological fracture but endoprosthetic replacement four months later due to confirmed IMWDOS by pathological findings with a follow-up duration of 101 months. The last patient had pelvic IMWDOS which was excised and followed up for 37 months.

Results

Imaging presentations

The lesion was located in the tibial proximal, middle and distal segments with involvement of fibula, the humerus proximal segment, the radius distal segment, the pelvis and acetabulum in seven patients. All the rest patients had the lesion in the femur, including the proximal segment in three patients and distal ends in the rest seven patients (Table 1 and Fig.1-6). In 16 cases with long bones diseases, the greatest diameter ranged 3.5-13.9 cm (mean 9.4), all involving the metaphysis region and nine cases having the lesion extending towards the diaphysis. The lesion was close to the lower joint surface (within 1 cm to the joint surface) in eight cases and across the joint surface in four cases. The lesion was primarily osteolytic in six patients (35.3%), osteosclerotic in two (11.8%) and mixed destruction in the rest (52.9%) (Table 2). The lesion was clearly separated from surrounding bone in only one patient but unclearly in the rest. The bone cortex was destructed and discontinued in all but one patient (Table 3). In one patient, the discontinued cortex was only demonstrated by CT scanning (Fig.2-6). The endosteum was invaded with thinned cortex in all patient accompanied with some irregularly thickened cortex (Fig.1&2). The lesion grew eccentrically in two patients but involved the whole medullary cavity in the rest with infiltrating destruction on one side of the bone. The lesion was markedly expansive in
six patients, non-expansive in three and eccentrically slightly expansive in the rest (Table 3). Bone septum was presented in the lesion in eight patients, with thick bone septum in six patients but thin septum in two. Variant ossification areas were shown in the lesion in 13 cases, and periosteal reaction was present in seven cases. One patient with the lesion in the middle and distal tibial segments had marked periosteal reaction with presence of Codman triangle, but the rest six patients had slight periosteal reaction. Except for the patient with the lesion in the distal radius segment and in the acetabulum which had apparent soft tissue masses (MRI showed more clearly in Fig.3, 4 and 6), the rest six patients had the lesion extending into surrounding soft tissue but with no apparent masses. In one patient with accompanied secondary aneurysmal bone cyst, MRI scanning showed apparent expansion with a fluid-fluid level. Pre-operation misdiagnosis was made in six patients as a benign lesion including fibrous dysplasia, aneurysmal bone cyst and giant cell tumor of bone in three patients, and the rest three patients all had a lesion of expansive growth with a relatively clear edge, which was diagnosed as a benign tumor. One lesion at the femoral proximal end was misdiagnosed as femoral head necrosis with cystic change.

Discussion

Most osteosarcomas are of high malignancy with marked cytological heterotype, whereas INWDOs is rare but has a more benign indolent course with a higher survival rate and less potential for metastasis. Local excision of this disease is almost always associated with recurrence leading to a high-grade common osteosarcoma in 15% of the patients. Consequently, it is crucial to distinguish the INWDOs from benign lesions and high-grade osteosarcomas.

In our study, we investigated the clinical, imaging and pathological data of 17 patients with IMWDOs. In this cohort of patients, the disease is more prevalent in the male than the female gender. This is quite different from the literature which has reported that the disease prevalence was equivalent in both genders or slightly more in female than in male gender. The age of the cohort in our study was greater than patients with common osteosarcoma, which is in line with the literature. Most of the lesions were located in long bones except for one case which was at the pelvis. The femoral lesions accounted for 62.5% of all the patients while the distal end of the femur accounted for 70% of all the cases. All the lesions in the long bones involved the metaphysis or mainly the metaphysis and diaphysis of the bone. The majority (52.9%) of radiographic patterns in our series were in line with the mixed osteolytic and osteosclerotic pattern, with the osteolytic pattern in only five patients and the osteosclerotic in three.

In imaging diagnosis, IMWDOs can be confused with fibrous dysplasia, desmoplastic fibroma, nonossifying fibroma, osteoblastoma and aneurysmal bone cysts. The key to distinguish IMWDOs from benign tumors is to identify the invasive growth pattern, and the radiological characteristics are variable with a mixed osteolytic and osteoblastic appearance, as demonstrated in our study. Four radiological patterns of IMWDOs have been described by Andreason et al with a case cohort of 70 patients: osteolytic with varying amounts of thick and coarse trabeculation (31%), predominantly osteolytic with few thin incomplete trabecula (30%), densely osteosclerotic (24%) and mixed osteolytic and osteosclerotic (14%). The majority (52.9%) of radiographic patterns in our series were in line with the mixed osteolytic and osteosclerotic pattern, with the osteolytic pattern in only five patients and the osteosclerotic in three. Analysis of the imaging features in this group of patients, the imaging is characterized as expansile and osteolytic destruction with tumor bone inside the lesion, discontinued bone cortex, and uneven thickness of bone cortex, which are in line with the pathology of the tumor. The IMWDOs tumor has low malignancy, slow growth and expansile imaging presentation, which make it difficult to differentiate from benign tumors. However, benign tumors have consistent growth with even thickness of expansile cortex of bone, whereas the IMWDOs has uneven thickness of the bone cortex and discontinued cortex of bone, reflecting the invasiveness nature of low malignancy tumor to normal tissues.
Fibrous dysplasia, non-ossifying fibroma, osteoblastoma, or other benign tumors may be easily be misdiagnosed as IMWDOS (Table 3).

The key to differentiation from these benign tumors lies in recognition of the invasive growth pattern of IMWDOS because these benign tumors rarely present with cortical destruction or soft tissue masses. Some intermediate tumors like giant cell tumors, aneurysmal bone cyst, and desmoplastic fibroma should also be differentiated from IMWDOS, and these intermediate tumors have the following characteristics of expansile growth, complete bone shell, rare ossification or calcification. Other malignant tumors should also be differentiated including chondrosarcoma, low-grade fibrosarcoma, common osteosarcoma, Ewing's sarcoma, lymphoma, and metastatic tumors. Chondrosarcoma, low-grade fibrosarcoma and IMWDOS are all of low grade malignancies. When chondrosarcoma is located within the medulla, the bone intima often presents scallop-like notch, and the lesion often has characteristic annular, semicircular and popcorn-like cartilage calcification, with typical long cartilage lobular signal on T2WI. Low-grade fibrosarcoma also has invasive growth features but no ossification nor calcification within the lesion. Common osteosarcoma, Ewing's sarcoma, and lymphoma have high malignancy and are characterized by bone destruction, periosteal reaction, soft tissue masses but rare expansion. Metastatic tumors often have multiple lesions besides the history of the primary tumor. When the IMWDOS lesion is primarily osteolytic, it should be differentiated from giant cell tumors, aneurysmal bone cyst, non-ossifying fibroma, fibrous dysplasia, desmoplastic fibroma, and low-grade fibrosarcoma. When the IMWDOS lesion is primarily osteosclerotic, it should be differentiated from osteoblastoma and sclerosing osteosarcoma. In mixed lesions, it should be differentiated from fibrous dysplasia, desmoplastic fibroma, osteoblastoma, and chondrosarcoma.

In conclusion, intramedullary well-differentiated osteosarcoma tends to occur at the metaphysis of long bones especially at the distal femur involving a large chance of cure.

There may be some limitations in this study, including a limited cohort of patients, which indicates the rarity of this disease, single center study, retrospective nature, Chinese ethnicity only and no comparison. However, this study also confirmed that wide excision with negative margins in most cases have a high chance of cure.

In conclusion, intramedullary well-differentiated osteosarcoma tends to occur at the metaphysis of long bones especially at the distal femur involving a large area. Histological, clinical and imaging data have to be closely combined to reach the correct diagnosis.

Declarations

- Ethics approval and consent to participate: This study was approved by the ethics committee of the Third Hospital of Hebei Medical University, and all patients had given their signed informed consent to participate.
- Consent for publication: All authors agreed to publish the paper in this journal.
- Competing interests: None.
- Funding: None.
- Acknowledgements: None.
- Availability of data and materials: All data and materials are available from the corresponding author on reasonable requirements.

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**Tables**

Table 1. Baseline and follow-up data of 17 patients with intramedullary well-differentiated osteosarcoma
| No./age | Site                          | SD (m) | Initial treatment | Recurrence | Re-treatment | Follow-up (m) | Follow-up outcome       |
|---------|-------------------------------|--------|-------------------|------------|-------------|---------------|------------------------|
| 1/45    | Left femur proximal segment  | 2      | C, ABG            | 8 m later  | no          | 20            | Metastasis, Dead       |
| 2/46    | Right femur intertrochanter   | 6      | WE; PR            | no         | no          | 6             | Alive, no recurrence or metastasis |
| 3/21    | Left femur distal end         | 4      | WE; PR            | no         | no          | 80            | Alive, no recurrence or metastasis |
| 4/52    | Left femur distal end         | 36     | Curettage         | 9 m later  | Knee joint replacement and chemotherapy | 32 | Metastasis, Dead |
| 5/36    | Right femur distal end        | Tramatic pathological fracture | Internal fixation and biopsy | no |Wide excision | 101 | Alive, no recurrence or metastasis |
| 6/21    | Left femur distal end         | 7      | Amputation        | no         | no          | 26 yr         | Alive, no recurrence or metastasis |
| 7/23    | Right femur distal end        | 8      | Amputation        | no         | no          | 26 yr         | Alive, no recurrence or metastasis |
| 8/27    | Right femur distal end        | 6      | C                | no         | no          | 45            | Alive, no recurrence or metastasis |
| 9/48    | Right tibia proximal segment | 5      | WE                | no         | no          | 8             | Alive, no recurrence or metastasis |
| 10/19   | Left tibia distal end         | 6      | C                | 6 m later amputation | no |28 | Dead |
| 11/20   | Right humerus proximal segment | Tramatic pathological fracture | WE; PR | no | no | 40 | Alive, no recurrence or metastasis |
| 12/35   | Left radius distal end        | 5      | WE, ABG          | no         | no          | 16            | Alive, no recurrence or metastasis |
| 13/28   | Acetabulum                    | 6      | Marginal excision | 2 yr       | Marginal excision | 37 | Alive, recurred thrice, no metastasis |
| 14/47   | Left tibia proximal end       | 12     | Knee prosthesis  | no         | No          | 27            | Alive, no recurrence or metastasis |
| 15/55   | Left femur proximal end       | 2      | Hip joint hemiarthroplasty | no | No | 5 | Alive, no recurrence or metastasis |
| 16/35   | Left tibial mid and distal segments | Curettage | 10 yr later | Left knee disarticulation | 120 | Alive, recurred once, no metastasis |
| 17/55   | Right femur distal end        | 9      | Knee prosthesis  | no         | no          | 2             | Alive, no recurrence or metastasis |

Note: SD, symptom duration; m, months; C: Curettage; WE: wide excision; ABG: autologous bone graft; PR: prosthesis replacement.

Table 2. Imaging presentations of the tumors in plain radiography, CT and MRI

| Imaging (n) | Unclear Margins | Periosteal reaction | expansile Sclerotic rim | Sclerotic Mixed destruction | Osteolytic sclerotic ossification | Discontinued cortex | Uneven cortex | Bone ridge | Soft tissue exte |
|-------------|-----------------|---------------------|-------------------------|-----------------------------|----------------------------------|---------------------|----------------|-----------|-----------------|
| X-Ray (17)  | 16/17           | 7/17                | 14/17                   | 7/17                        | 10/17                            | 6/17                | 3/17           | 13/17      | 15/17           | 16/17          | 8/17          | 8/17          |
| CT (14)     | 13/14           | 6/14                | 12/14                   | 4/14                        | 7/14                             | 5/14                | 2/14           | 13/14      | 13/14           | 14/14          | 7/14          | 7/14          |
| MRI (9)     | 0/9             | —                   | 8/9                     | 2/9                         | —                                | —                   | —              | —          | 9/9             | 9/9            | 6/9           | 6/9           |

Note: CT, computed tomography; MRI, magnetic resonance imaging.

Table 3. Differential diagnosis of well-differentiated osteosarcoma in 17 patients
| No./age | Site                          | Bone destruction | Rims    | Cortical destruction | Expansion | Bone ridge | Ossification | Periosteal reaction | Soft tissue mass | Preoperative differentiation |
|---------|-------------------------------|------------------|---------|----------------------|-----------|------------|--------------|---------------------|-----------------|-------------------------|
| 1/45    | L femur, proximal segment     | Mixed            | Unclear | Yes                  | Marked    | Coarse     | Yes          | No                  | No              | Desmoplastic fibroma    |
| 2/46    | Rt femur, intertrochanter     | Osteogenic       | Unclear | Yes                  | No        | No         | Yes          | No                  | No              | Sclerosing osteosarcoma  |
| 3/21    | L femur, distal end           | Osteolytic       | Unclear | Yes                  | Marked    | Coarse     | Yes          | Slight              | No              | Aneurysmal bone cyst     |
| 4/52    | L femur, distal end           | Mixed            | Unclear | Yes                  | Marked    | Coarse     | Yes          | Slight              | No              | Chondrosarcoma           |
| 5/36    | Rt femur, distal end          | Mixed            | Unclear | Yes                  | Slight    | No         | Yes          | Slight              | No              | Fibrous dysplasia        |
| 6/21    | L femur, distal end           | Osteolytic       | Unclear | Yes                  | Marked    | Coarse     | Yes          | No                  | No              | Desmoplastic fibroma     |
| 7/23    | Rt femur, distal end          | Mixed            | Clear   | Yes                  | Marked    | No         | Yes          | No                  | No              | Osteoblastoma            |
| 8/27    | Rt femur, distal end          | Osteolytic       | Unclear | Yes                  | Slight    | Yes        | No           | No                  | No              | Desmoplastic fibroma     |
| 9/48    | Rt tibia, proximal segment    | Mixed            | Unclear | Yes                  | Slight    | No         | Yes          | Slight              | No              | Osteosarcoma             |
| 10/19   | L tibia, distal end           | Osteolytic       | Unclear | Yes                  | Slight    | slight     | No           | No                  | No              | Low grade fibrosarcoma   |
| 11/20   | Rt humerus, proximal segment  | Mixed            | Unclear | Yes                  | No        | Coarse     | Yes          | Slight              | No              | Fibrous dysplasia        |
| 12/35   | L radius, distal end          | Osteolytic       | Unclear | Yes                  | Marked    | Coarse     | No           | No                  | Marked           | Giant cell tumor         |
| 13/28   | L area, acetabulum            | Mixed            | Unclear | Yes                  | Slight    | No         | Yes          | slight              | Marked           | Chondrosarcoma           |
| 14/47   | L tibia, proximal end         | Osteogenic       | Unclear | No                   | No        | No         | Yes          | No                  | No              | Sclerosing osteosarcoma  |
| 15/55   | L femur, proximal end         | Osteolytic       | Unclear | Yes                  | Slight    | No         | Yes          | No                  | No              | Femoral head necrosis    |
| 16/35   | L tibia, distal segment       | Mixed            | Unclear | Yes                  | Slight    | No         | Yes          | Marked              | No              | Common osteosarcoma       |
| 17/55   | Rt femur, distal end          | Mixed            | Unclear | Yes                  | Slight    | slight     | Yes          | slight              | No              | Fibrous dysplasia        |