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Sarcomatous change in the Pagetoid tibiae

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Abstract We reviewed 13 cases of tibial Paget's sarcoma constituting 14% of all registered Paget's sarcoma cases of the Scottish Bone Tumour Registry between January 1947 and June 2004. Eleven patients were male, and in ten patients the tumour involved the upper half of the tibia. In all cases, the main presenting feature was progressively worsening pain followed by a mass in six, a pathological fracture in five and tibial bowing in four. In nine patients, a lytic lesion was seen radiologically. Histologically, there were three osteosarcomas and ten malignant fibrous histiocytomas. Limb ablation was carried out in 11 patients, of whom nine had trans-femoral amputation. Six patients received adjuvant radiotherapy and/or chemotherapy. Post-operative complications included stump revision in two cases, non-union of a pathological fracture of the tibial tuberosity and a stress fracture. The median survival was 17 months.

Résumé Nous avons examiné 13 cas de sarcome tibial sur Paget, représentant 14% de tous les sarcomes sur Paget enregistrés dans le registre écossais des tumeurs osseuses entre janvier 1947 et juin 2004. Onze malades étaient de sexe masculin et, chez dix malades la tumeur a impliqué la moitié supérieure du tibia. Les symptômes étaient une douleur progressivement croissante dans tous les cas, une masse dans six cas, une fracture pathologique dans cinq cas et une courbure progressive du tibia dans quatre cas. Chez neuf malades une lésion ostéolytique a été vue radiographiquement. Il y avait histologiquement trois ostéosarcomes et dix histiocytofibromes malins. Une amputation a

était faite chez 11 malades, 9 fois à un niveau trans-fémoral. Six malades ont reçu une radiothérapie et/ou chimiothérapie adjuvante. Les complications postopératoires ont inclus la révision du moignon dans deux cas, la pseudarthrose d'une fracture pathologique de la tubérosité tibiale et une fracture de fatigue. La survie médiane était de 17 mois.

Introduction

Sarcomatous degeneration is a rare complication of Paget's disease of bone. Although tibia is a well-known site for Paget's disease, sarcomatous degeneration is relatively uncommon at this site compared with femur, pelvis, humerus and skull [7, 12].

While there is ample literature on the clinico-pathological aspects of Paget's sarcoma [2–6, 9, 10], there is no published evidence focusing on the biological behaviour of Paget's sarcoma of the tibia. In addition, this part of the body is more amenable to an early limb ablative procedure, with a better chance of early rehabilitation and possible better prognosis. There could be a diagnostic dilemma in some patients with Paget's sarcoma of the tibia. In this series, we analysed the detailed clinical, radiological and histological features of 13 patients with Paget's sarcoma of the tibia in order to evaluate whether the biological behaviour of the tumour in this particular anatomical location is any different from Paget's sarcoma in general.

Methods and materials

Of the total 90 cases of Paget's sarcoma registered in the Scottish Bone Tumour Registry, 13 cases of tibial Paget's sarcoma between January 1947 and June 2004 were accrued. This registry is a prospective database, which updates follow-up data of patients by obtaining information from orthopaedic/oncology/surgical clinics and communication from general practitioners.

Case notes, radiographs and histological sections were reviewed in order to analyse the variables viz. age, gender,

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Table 1 Detailed description of sarcoma of the tibia in Paget's disease

Patient no.	Age/ gender/ side	Site	Type of Paget's disease	Duration of symptom prior to presentation	Clinical presentation	Plain X-ray	Duration between presentation and diagnostic biopsy	Type of presentation biopsy	Surgical treatment	Radiotherapy	Survival
1	76/M/R	Lower mid third	Polyostotic (skull, pelvis)	8 months	Right leg deformity, history of trauma + lytic	Predominantly lytic	–	–	Above-knee amputation	–	80 months
2	60/M/R	Lower third	Monostotic	11 months	Right painful swollen ankle, tibial bowing deformity	Predominantly lytic	<1 week	Open	Above-knee amputation	–	23 months
3	74/M/L	Upper third	Polyostotic (skull, 6 weeks pelvis, scapula, bifemori)	6 weeks	Painful lump upper leg	Predominantly lytic	<1 week	Open	–	Radical orthovolt 6,200 rads, palliative 4-drugs chemotherapy	35 months
4	60/M/R	Upper mid third	Polyostotic (spine, pelvis)	6 weeks	Painful right knee, pathological fracture	Mixed	1 week	Open	Through-knee amputation	–	12 months
5	68/M/L	Upper third	Polyostotic (skull, 3 months pelvis, lumbar spine, femur)	3 months	Painful lump upper leg, pathological fracture	Predominantly lytic	–	–	Above-knee amputation, complicated by flap necrosis, revision amputation	Adjuvant 2-drugs chemotherapy	17 months
6	72/M/L	Lower third	Monostotic	5 months	Painful lump lower leg, tibial bowing deformity	Predominantly lytic	<1 week	Open	Below-knee amputation with inguinal lymph node resection, 2nd stage, below-knee amputation	Neo-adjuvant 5,400 rads, adjuvant 2,700 rads	11 months
7	57/M/L	Upper third	Polyostotic (shoulder, ilium)	6 weeks	Painful lump upper leg	Predominantly lytic	<1 week	Open	Above-knee amputation	Adjuvant 2-drugs chemotherapy	168 months
8	81/F/R	Upper two third	Monostotic	4 days	Pain upper leg, pathological fracture	Predominantly lytic	–	–	Above-knee amputation; also had pathological fracture left neck of femur 3 weeks postop, treated with dynamic hip screw	–	2 months

Table 1 (continued)

Patient no.	Age/ gender/ side	Site	Type of Paget's disease	Duration of symptom prior to presentation	Clinical presentation	Plain X-ray	Duration between presentation and diagnostic biopsy	Type of biopsy	Surgical treatment	Radiotherapy	Survival
9	66/M/L	Upper third	Polyostotic (pelvis, femur, right calcaneus, spine-D11-L3), multifocal-os calcis and spine	1 day	Sudden severe pain, pathological fracture, developed complete paraplegia with sacral sores 7 weeks post-fracture	Predominantly lytic	–	–	Above-knee amputation, local recurrence 8 months later	Palliative radiotherapy	13 months
10	70/F/R	Upper third	Monostotic	4 months	Painful lump upper leg, tibial bowing deformity	Predominantly sclerotic	4 months	Open	Above-knee amputation	–	19 months
11	64/M/R	Upper third	Polyostotic (spine, skull, femur)	1 day	Pain and pathological fracture of tibial tuberosity	Predominantly lytic	<1 week	Open	Open reduction internal fixation of avulsion fracture, non-union, stress fracture	Radical orthovolt 6000 rads, Palliative chemotherapy	28 months
12	72/M/L	Upper third	Polystotic (skull, femur, patella)	10 days	Increasing pain only	Predominantly sclerotic	<1 week	Open	Above-knee amputation	–	10 months
13	76/M/L	Upper mid third	Monostotic	2 weeks	Increasing pain, expanding calf haematoma	Predominantly lytic	<1 week	Open	Above-knee amputation	–	2 months

site, type of Paget's disease (monostotic or polyostotic), duration of symptoms prior to seeking medical attention, mode of clinical presentation, diagnosis of metastasis at diagnosis and radiological features. Biopsy, histological type and grade, mode of treatment, role of adjuvant therapy and survival were evaluated.

Tibial Paget's sarcoma cases constituted 14.4% of all registered Paget's sarcoma cases. The mean age was 68.9 (range, 57 to 81 years). There were 11 male and two female patients. Six were right-sided and seven left-sided. There were eight polyostotic and five monostotic cases. Ten out of 13 occurred in the upper half of the tibia, of which three fourths predominantly involved the upper third of tibia.

Eleven of 13 patients had undergone limb ablation procedure. All limb ablation procedures were carried out with >5 cm clear oncological margins. The adequacy of the resection margins was confirmed by the pathological specimen. There were two patients who were not ablated: case 3 was unfit for limb ablation procedure and was treated with high-dose radiotherapy/chemotherapy; case 11 underwent open reduction and internal fixation of pathological avulsion fracture of the tibial tuberosity.

Results

Clinical features are summarised in the Table 1. Four patients presented with acute onset of symptoms between 1 and 10 days. Sub-chronic onset of symptoms (up to 6 weeks) was observed in four patients. In the remaining five, the duration symptoms varied from 3 to 11 months. Progressively worsening pain was the main presenting feature in all cases. In addition, five cases had a lump, five had pathological fractures and four had tibial bowing. Out of five pathological fractures, one patient with a pathological fracture of the tibial tuberosity

underwent open reduction and internal fixation followed by irradiation but subsequently developed non-union and stress fracture (Fig. 1a and b). Four cases of pathological fractures had pain without any lump. One patient had a rapidly progressing expanding calf haematoma.

Alkaline phosphatase levels were from 29 to 1093 U (normal range, 20–260 U). Erythrocyte sedimentation rate ranged from 8 to 64. Ten out of 13 patients had predominantly lytic appearance on plain radiographs (Fig. 2a and b). There were two predominantly sclerotic cases while one case showed a mixed (both sclerotic and lytic) pattern (Fig. 3). Radiological features were characterised by cortical destruction ($n=8$), soft tissue mass ($n=6$), bone expansion ($n=11$) and bowing ($n=4$). Five patients had a bone scan, one of which was positive for single focus and the rest had hot spots at multiple foci. The oncological staging (chest radiograph and/or CT chest) confirmed presence of pulmonary metastases in three out of 13 patients at the time of diagnosis.

Nine patients had open diagnostic biopsy prior to the operative intervention. Eight out of nine had their biopsy performed within 1 week of presentation while one had to wait for 4 months due to investigations performed on an outpatient basis, as Paget's sarcoma was not suspected initially in this case. Four patients had limb ablative procedures based on clinico-radiological findings of Paget's sarcoma, which were subsequently confirmed by the histological evidence of Paget's sarcoma in the amputated specimen. Histology diagnosed osteosarcoma ($n=3$) and malignant fibrous histiocytoma ($n=10$). Histological details are described in Table 2.

Limb ablation was carried out in 11 patients; nine had trans-femoral/above-knee amputation, one trans-articular/through-the-knee and one trans-tibial/below-knee. One patient was treated with high-dose radiotherapy only as this

Fig. 1 **a** Anteroposterior radiograph, and **b** lateral radiograph revealing pathological avulsion fracture of the tibial tuberosity treated with tension-band wiring. Note the sarcomatous bone destruction in the Pagetoid bone

Fig. 2 **a** Antero-posterior radiograph, and **b** lateral radiograph revealing predominantly lytic distal tibial involvement with Paget's sarcoma

patient was anaesthetically assessed to be medically unfit for the limb ablation procedure. Stump revision was done in two cases for flap necrosis and local recurrence. Non-union of a pathological fracture of the tibial tuberosity and stress fracture in the irradiated bone occurred in one patient. Six cases received adjuvant radiotherapy/chemotherapy, four had palliative chemotherapy (two-to-four drugs, namely adriamycin, cyclophosphamide, melphalan, vincristine) and four had palliative radiotherapy (2,700–6,200 rads) alone. The rationale for adjuvant radiotherapy/chemotherapy was to achieve better local/systemic control by killing the remaining tumour load after limb ablation.

Median survival was 17 months (1-year 61.5%, 2-year 30.7% and 5-year 15.3%). Survival with surgical treatment only was 24.3 months. Survival with surgical treatment and adjuvant radiotherapy/chemotherapy was 47.4 months. Death was due to metastases in ten patients (including three at presentation) and related to persistent primary disease in one patient. Two patients died of unrelated causes.

Discussion

This is a largest clinico-radiological and histopathological review of 13 cases of sarcoma complicating Paget's disease

of the tibia from a tertiary oncology unit of the UK. This study highlighted the fact that tibial Paget's sarcomas are largely monofocal, arising from polyostotic Paget's disease. They typically exhibit a lytic radiological pattern, and malignant fibrous histiocytoma is the predominant histological type. Limb ablative procedure is the mainstay of local control and the median survival is 17 months.

The common presenting symptoms are progressive pain, mass with or without pain, and a pathological fracture. There was no evidence in these cases that malignant transformation occurred at the site of a former fracture. Five patients had pathological fractures, of whom four were treated by conservative means initially, and one underwent open reduction and internal fixation for pathological fracture of the tibial tuberosity. One patient had a rapidly progressing, expanding, calf haematoma (case 13). Erlich et al. reported a case of bilateral synchronous Paget's sarcomas in the tibiae, which developed in the upper right tibia and in the distal third of the left tibia. Upward spread of the tumour in the left tibia occurred dramatically in the soft tissue and only involved the medullary cavity in its inferior portion [1]. There were no bilateral cases in this series. Resnick et al. published a case where a patient with Paget's disease presented with a soft tissue mass formation from the tibia [8]. As patients with Paget's disease of bone are not registered in the Scottish Bone Tumour Registry, it is dif-

Fig. 3 Antero-posterior and lateral radiographs revealing tibial bowing and mixed appearance in the mid-shaft of the tibia due to sarcomatous change

Table 2 Histological details of the sarcoma of the tibia in Paget's disease

Number	Histopathological evidence of Paget's disease of bone	Type of sarcoma	Comments
1	Yes	MFH (malignant fibrous histiocytoma)	Fibrosarcomatous, no osteoid
2	Yes	MFH	High-grade sarcoma, no osteoid, prominent giant cells
3	Yes	MFH	High-grade sarcoma, no osteoid
4	Yes	MFH	Fibrosarcomatous, no osteoid
5	Yes	MFH	Fibrosarcomatous, no osteoid
6	Yes	Osteosarcoma	–
7	Yes	Osteosarcoma	–
8	Yes	MFH	High-grade sarcoma, no osteoid
9	Yes	MFH	Pleomorphic spindle cell sarcoma
10	Yes	MFH	High-grade sarcoma, no osteoid
11	No pre-existing bone	MFH	High-grade sarcoma, no osteoid
12	Yes	Osteosarcoma	–
13	Yes	MFH	High-grade sarcoma, vascular invasion

difficult to comment on whether there is a higher chance of malignant transformation in tibial lesions.

The level of alkaline phosphatase is not a reliable tumour marker. An abrupt elevation of alkaline phosphatase should alert the clinician to the possibility of malignant transformation of a Pagetic lesion; however, the degree of elevation is variable, as observed in this series. Plain X-ray findings of Paget's disease are cortical thickening, loss of cortico-cancellous differentiation and enlargement of the bone with a flame-shaped area of radiolucency. A predominantly lytic area of bone destruction on plain radiographs is typical of Paget's sarcoma [5, 6, 10]. Roentgenographic changes of a sarcomatous change are difficult to identify on plain films in the early stages, and consequently, CT-scan studies are recommended whenever a sarcoma is suspected. CT findings include moth-eaten, vacuolar, network, clumped, fibrillary or ivory images of destruction. Reduced T1-weighted marrow signals in MRI scan is a typical but non-specific feature of Paget's sarcoma [11]. CT and MRI scans were only carried out in the last four cases in this series and were consistent with the above-mentioned, non-specific features of bone destruction and soft tissue extension. The radiological features were predominantly characterised by cortical destruction ($n=8$) and soft tissue mass ($n=6$) in this study.

In this small series, malignant fibrous histiocytoma was the predominant histological type. This is in contrast to the published literature where osteosarcoma is the most common type [2, 10, 12]. Historically, the exact distinction between malignant fibrous histiocytoma and osteosarcoma has been difficult. On initial review, six cases were diagnosed as osteosarcoma and seven were malignant fibrous histiocytoma. Subsequent re-evaluation of pathology specimens confirmed malignant fibrous histiocytoma in ten cases and only three cases of osteosarcoma. This salient histological finding could be related to the localisation of malignant transformation in the tibia.

Amputation was the mainstay of local control in this series. Radiotherapy and chemotherapy were mainly prescribed as an adjuvant therapy. In this series, survival after surgical intervention combined with adjuvant radiotherapy/chemotherapy was 47.4 months. It was better than survival with surgical treatment/limb ablation alone (24.3 months). Paget's sarcoma is relatively resistant to radiation therapy and chemotherapy, and there is no curative treatment. The rationale for using the adjuvant treatment modalities in some of these patients was mainly aimed at better clearance of the systemic tumour load (micro-metastasis) after limb ablation.

Paget's sarcoma is a rapidly fatal condition. Elderly patients, predominance of osteogenic sarcoma, increased risk of sarcoma in polyostotic Paget's disease and a very poor prognosis are typically documented in the literature [7, 9, 12]. Whilst in agreement with the previous evidence that sarcomatous change in Paget's disease of bone has an overall poor prognosis, we found a median survival of 17 months with predominantly malignant fibrous histiocytomatous histology. Case no. 7 is one of the longest survivors following Paget's sarcoma of tibia (168 months). We found that Paget's sarcoma of the tibia is characterised by predominantly monofocal sarcoma arising from polyostotic Paget's disease in the majority of patients. Radiologically it is typically lytic and the histology is predominantly malignant fibrous histiocytoma. It is amenable to early limb ablative procedures. We emphasise the need for further research by a combined genetic, molecular biological, oncological, surgical, radiological and histological approach to obtain better local control and to improve the overall prognosis. This could be best achieved by gathering data from multiple centres in view of the rarity of the condition.

[3], [4].

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