Distinguishing bone and soft tissue infections mimicking sarcomas requires multimodal multidisciplinary team assessment

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ABSTRACT

INTRODUCTION The aims of this study were to report the presenting characteristics and identify how best to distinguish bone and soft-tissue infections that mimic sarcomas.

MATERIALS AND METHODS A total of 238 (211 osteomyelitis and 27 soft-tissue infections) patients referred to a tertiary sarcoma multidisciplinary team with suspected sarcoma who were ultimately diagnosed with a bone or soft tissue infection were included. Data from a prospectively collated database was analysed retrospectively.

RESULTS Of all possible bone and soft-tissue sarcoma referrals, a diagnosis of infection was made in 2.1% and 0.7%, respectively. Median age was 18 years in the osteomyelitis group and 46 years in the soft-tissue infection group. In the osteomyelitis group, the most common presenting features were pain (85.8%) and swelling (32.7%). In the soft-tissue infection group, the most common clinical features were swelling (96.3%) and pain (70.4%). Those in the soft-tissue group were more likely to have raised inflammatory markers. Radiological investigations were unable to discern between tumour or infection in 59.7% of osteomyelitis and 81.5% of soft-tissue infection cases. No organism was identified in 64.9% of those who had a percutaneous biopsy culture.

CONCLUSIONS This study has highlighted that infection is frequently clinically indistinguishable from sarcoma and remains a principle non-neoplastic differential diagnosis. When patients are investigated for suspected sarcoma, infections can be missed due to falsely negative radiological investigations and percutaneous biopsy. As no single clinical, biochemical or radiological feature or investigation can be relied upon for diagnosis, clinicians should have a low threshold for tissue biopsy and discussion in a sarcoma multidisciplinary team meeting.

KEYWORDS

Infection – Bone diseases – Muscular diseases – Neoplasms – Connective and soft tissue – Diagnostic techniques and procedures

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Introduction

Sarcomas are rare malignant tumours of mesenchymal origin accounting for less than 1% of all malignant neoplasms.¹ They are typically aggressive and are associated with an overall five-year survival of approximately 56% for bone sarcomas and 54% for soft tissue sarcomas.² The most common presenting symptoms for bone and soft tissue sarcomas are pain and swelling. However, these are also the primary features of inflammatory, benign neoplastic and infective conditions, rendering a clinical diagnosis difficult. Consequently, expedient and accurate diagnosis mandate the involvement of several clinical specialties.

The differential diagnosis for osseous lesions in patients with pain and/or swelling is wide and includes benign and malignant tumours, pseudo-tumours (eosinophilic granuloma), and osteomyelitis. Osteomyelitis can occur acutely,

sub-acutely or chronically, arbitrarily referring to infections lasting weeks, one to three months and more than three months, respectively.³ With time, contained purulent collections can form abscesses within the bone.³ In patients with a soft-tissue mass, the differential diagnoses include benign and malignant tumours, fluid collections (haematoma, abscess) and granulomatous infections.⁴

Narrowing the differential diagnosis is complicated by two further factors. First, both primary bone tumours and osteomyelitis have a preponderance in children and young adults, so age does not help to limit the differential diagnosis.^{5,6} Second, infection and tumour may, rarely, coexist.^{7,8} The underlying diagnosis of a presentation of pain and swelling may thus be unclear. Indeed, one report found that 50% of all cases of sub-acute osteomyelitis in children are initially confused with tumour.⁹ Investigations typically include blood tests for the acute phase response, imaging

including radiographs and magnetic resonance imaging (MRI) and, ultimately, biopsy with culture and histopathological assessment.^{10,11}

There have been reports of infections mimicking and potentially delaying the diagnosis of a malignancy. However, to our knowledge, there are few reports describing the rate and presentation of patients with infection who initially presented with features suggestive of a tumour.¹² We report on patients referred to our tertiary sarcoma centre with suspected bone or soft-tissue tumours who were subsequently diagnosed with infection of the bone or soft tissues. We aimed to identify the common clinical features and accuracy of biochemical, radiological and biopsy investigations that led to a diagnosis of infection when referral queried malignancy.

Materials and methods

We performed a retrospective analysis of a prospectively collected database of 40,800 patients referred to an orthopaedic oncology service between 1987 and 2016. Patients with a diagnosis of infectious aetiology were identified and notes reviewed to determine whether the referral working diagnosis was sarcoma. All included patients were discussed and diagnosed by a multidisciplinary team comprising orthopaedic oncologists, musculoskeletal radiologists and sarcoma histopathologists.

We identified 484 patients referred with suspected sarcoma who were subsequently diagnosed with an infection. The infective diagnoses included osteomyelitis (381 patients) and soft-tissue infections (103 patients). In the osteomyelitis group, 170 patients were excluded because of incomplete data, specifically lack of complete blood tests ($n = 133$), radiology reporting ($n = 14$) or patients with an eventual diagnosis of chronic recurrent multifocal osteomyelitis ($n = 23$). In the soft-tissue group, 76 patients were excluded for incomplete data, specifically lack of complete blood tests ($n = 53$) and radiology reports ($n = 23$). Therefore, 211 patients with osteomyelitis and 27 patients with soft-tissue infection were included. During the same period, we received a total of 18,378 suspected bone tumour referrals and 13,988 suspected soft tissue sarcoma referrals.

Patient records were reviewed to retrieve patient demographics as well as clinical, radiological, histological and microbiological information. The inflammatory acute phase response was determined by white cell count (WCC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels. Imaging included plain film radiographs and MRI. Tissue biopsy was performed using a percutaneous Jamshidi™ biopsy technique as per the European Society for Medical Oncology and British Sarcoma Group Guidelines.^{13–16} The needle core was then swabbed and sent to microbiology for gram stain and culture (for aerobic, anaerobic and acid fast bacilli) and pathology for histological analysis. Patients were excluded if they had not been clinically assessed at our institution or if they were referred with a working diagnosis other than

sarcoma. Statistical analysis was performed using Deducer¹⁷ and R¹⁸ statistical software packages, and statistical significance was considered to be $P < 0.05$.

Results

Osteomyelitis

The 211 osteomyelitis cases had a median age of 18 years (interquartile range, IQR, 11–36 years) at diagnosis (Figure 1). There were 123 (58.3%) men and 88 (41.7%) women. The most common sites were the femur ($n = 57$, 27.0%), tibia ($n = 49$, 23.2%), clavicle ($n = 28$, 13.3%) and pelvis ($n = 24$, 11.4%; Table 1). A diagnosis of osteomyelitis was made in 2.1% of all bone tumour referrals (381 cases in 18,378 referrals during the study period). Referrals came from orthopaedic surgeons in 70.3%, general practitioners in 17.6%, accident and emergency practitioners in 6.0% and other secondary care specialists in 6.1% of cases.

Nearly all patients presented after exhibiting symptoms ($n = 208$, 98.6%). Pain was the most common presenting symptom, in 181 patients (85.8%), followed by swelling, ($n = 69$, 32.7%). Only 19 patients (9.0%) presented with features of systemic involvement, such as pyrexia, lethargy, poor appetite and malaise. Eight individual patients presented with erythema ($n = 8$, 3.8%) and pathological fracture ($n = 8$, 3.8%). Three patients (1.4%) were asymptomatic and were referred for incidental radiological findings consistent with primary bone sarcoma (Figure 2).

At presentation, the median WCC was $7.8 \times 10^9/l$ (IQR 6.4 – $9.5 \times 10^9/l$), the median CRP level was 4 mg/l (IQR 2–19.25 mg/l) and the median ESR was 15 mm/hour (IQR 7–34.25 mm/hour). Of the recorded CRP results, 96 (45.5%) were less than 3 mg/l, the lowest recordable result (Figure 3).

Reporting of radiological investigations by specialist musculoskeletal sarcoma radiologists identified that 53.1% of cases ($n = 112$) the diagnosis was unclear (i.e. could not rule out tumour), in 40.3% of cases ($n = 85$) infection was the most likely diagnosis and in 6.6% of cases ($n = 14$) the

Table 1 Anatomical sites of osteomyelitis.		
Site of infection	Patients (N = 211)	
	(n)	(%)
Femur	57	27.0
Tibia	49	23.2
Clavicle	28	13.3
Pelvis	24	11.4
Humerus	15	7.1
Ulna	9	4.3
Foot	9	4.3
Radius	5	2.4
Hand	5	2.4
Fibula	4	1.9
Other sites	6	2.8

most likely diagnosis was sarcoma but infection remained a possibility. The radiological features were in keeping with Ewing's sarcoma in 25 reports (11.8%), bone sarcoma not otherwise specified in 12 (5.7%), Langerhans cell histiocytosis in 5 (2.4%) and lymphoma in 9 (4.3%).

Of the 211 patients with osteomyelitis, 198 (93.8%) underwent biopsy and histological analysis. There was no growth on culture in 128 of the 198 patients (64.6%). *Staphylococcus aureus* was grown in 33 patients (16.7%) and acid fast bacilli/*Mycobacterium tuberculosis* were identified in 16 patients (8.1%). Other organisms were identified in 21 patients (10.6%), including *Streptococcus*, *Enterococcus*, *Proteus*, *Corynebacterium*, *Bacteroides*, *Fusobacterium* and *Haemophilus* (Table 2). In nine patients

Table 2 Culture results for all biopsies, osteomyelitis and soft-tissue infection cases.

Organisms	All tissue (N = 222)		Osteomyelitis (N = 198)		Soft-tissue infection (N = 24)	
	(n)	(%)	(n)	(%)	(n)	(%)
No organism identified	144	64.9	128	64.6	16	66.7
<i>Staphylococcus aureus</i>	36	16.2	33	16.7	3	12.5
Acid fast bacilli/ <i>Mycobacterium tuberculosis</i>	20	9.0	16	8.1	4	16.7
Other	22	9.9	21	10.6	1	4.1

Table 3 Anatomical sites of soft tissue infections.

Anatomical site	Soft-tissue infections (N = 27)	
	(n)	(%)
Thigh	10	37.0
Arm	6	22.2
Chest wall	4	14.8
Groin	2	7.4
Calf	1	3.7
Forearm	1	3.7
Other	3	11.1

(4.3%), a second biopsy was required as the first was non-diagnostic and, of those second biopsies, five were open/excisional biopsies.

Soft-tissue infections

Of the 27 patients diagnosed with a soft-tissue infection, the median age was 46 years (IQR 27.5–56 years) (Figure 1). There were 13 (48.1%) male and 14 (51.9%) female patients. The most common sites were the thigh, 10 patients (37.0%), upper arm, 6 patients (22.2%), chest wall, 4 patients (14.8%; Table 3). A diagnosis of soft-tissue infection was made in 0.7% of all potential soft tissue sarcoma referrals (103 cases in 13,988 referrals). Referrals were made by general practitioners in 45.5% of cases, orthopaedic surgeons in 40.9% and other specialities in 13.6%.

The most common presenting features were swelling, in 26 patients (96.3%), followed by pain in 19 patients (70.4%). Other features exhibited were skin changes (including erythema or discharge) in 2 patients (7.4%) and systemic symptoms were described by another 2 patients (7.4%; Figure 2).

The median WCC was $9.25 \times 10^9/l$ (IQR 7.7 – $10.4 \times 10^9/l$), median CRP was 23 mg/l (IQR 10–52 mg/l) and

the median ESR was 33 mm/hour (IQR 15–74 mm/hour; Figure 4). Only three patients (11.1%) had CRP results of less than three, the lowest recordable result.

Reporting of radiological investigations by specialist by musculoskeletal radiologists revealed that in 70.4% of cases ($n = 19$) the diagnosis was unclear (could not rule out tumour), in 18.5% of cases ($n = 5$) infection was the likely diagnosis, and in 11.1% of cases ($n = 3$) the likely diagnosis was malignancy. When tumour was considered on imaging, soft tissue sarcoma was mentioned in 10 reports (37.0%) and lymphoma and peripheral nerve sheath tumour were considered in one case each (3.7%).

Tissue biopsy was performed in 24 patients with soft-tissue infection (88.9%). When microbiology culture and results were reported, no organism was identified in 16 cases (66.7%). The most common organism isolated was acid fast bacilli/*M. tuberculosis* in four cases (16.7%), followed by *S. aureus* in three cases (12.5%; Table 2).

Discussion

Bone and soft-tissue sarcoma mimicking the presentation of infection has been widely reported in the literature.^{5,19–21} This scenario has also been associated with a delay in the commencement of treatment.²² However, there is a paucity of data comparing the reverse; presentation of patients referred with possible sarcoma that are subsequently diagnosed with an infection.¹² The purpose of this study was to specifically look at the features of clinical presentation and accuracy of biochemical, radiological and biopsy investigations for bone and soft-tissue infections when referred as a possible sarcoma.

In this study, the incidence of osteomyelitis when patients were referred for possible bone sarcoma was relatively high, at 2.1%, compared with a rate of 0.7% for soft-tissue infections originally believed to be soft-tissue sarcomas. Patients with osteomyelitis tend to be younger, with a median age of 18 years, in contrast to those with soft-tissue infections, who had a median age of 46 years. The most frequent anatomical sites for osteomyelitis are similar to those of primary bone sarcomas, including the femur, tibia, pelvis and humerus, however, the clavicle was found to be a common site for infection, an uncommon site for primary

bone sarcoma.⁶ The common sites for soft-tissue infections mimicking soft-tissue sarcomas were the thigh, arm and chest wall, again, common anatomical sites for sarcomas. Other data indicate that the most common anatomical sites for soft-tissue sarcomas are the limbs (25%), followed by the connective tissue of the trunk (15%).²³

With regards to the clinical presentation, pain was the most prevalent symptom in patients with osteomyelitis, whereas swelling was most the prevalent in soft tissue infections. However, it is important to note that pain was also a common feature of soft-tissue infections (70%), whereas soft-tissue sarcomas typically present as painless masses.¹¹ Notably, systemic upset was only noted in 9.0% and 7.4% of patients with bone and soft-tissue infections, respectively. Unfortunately, these signs and symptoms are also the main features of sarcoma.^{15,16} Therefore, based on the clinical presentation and anatomical location, it is impossible to distinguish sarcoma from infection.

Blood tests to identify an acute phase response (raised WCC, CRP and ESR) are collected when an infection is considered. However, in this study, WCC, CRP and ESR values were of limited use when trying to discern either bone or soft-tissue infections from sarcoma. For bone infections, ESR was raised in just over one-third of cases. Generally, there was a greater proportion of patients with evidence of an acute inflammatory response in those with soft-tissue infections, with 77.8% having a CRP level greater than 10

(normal: less than 5). There is typically a marked acute phase response in bone and soft-tissue infections. However, this study found that, when presenting to an oncological service, this relationship is not as strong, making diagnosis more difficult. While there has been an association between CRP elevation and soft-tissue sarcoma documented in the literature, this is more with regard to prognosis than diagnosis.^{24,25}

Radiological investigations included plain film radiographs and MRI. Surprisingly, in 59.7% of osteomyelitis cases and 81.5% of soft-tissue infection cases, imaging investigations were either unclear between tumour and infection or the diagnosis of tumour was considered the most likely. Differentiating bone or soft-tissue infection from malignancy solely based on imaging is also difficult and there are reports trying to identify features specific to each disease entity.^{26,27} Notably, periosteal reaction should not be assumed to be associated with a malignancy if read on a radiology report.²⁷ Therefore, nearly all patients, 95.8% and 88.9% in the osteomyelitis and soft-tissue infection groups, respectively, had a tissue biopsy and required complete multidisciplinary involvement to rule out tumour and diagnose infection. A majority of the patients in this series had subacute or chronic, low-grade infections, as those with acute infections were likely to have been more easily recognised and treated locally, not mimicking sarcoma and being referred to an oncology service.

An open tissue biopsy with curettage, and culture and sensitivity is the gold-standard method to diagnosis both osteomyelitis and soft-tissue infections. However, in this series, biopsies were obtained through a percutaneous approach to rule out malignancy, lowering their diagnostic yield for infection. In this specific set of patients, it was uncommon to receive a positive culture result, which occurred in only 35.4% and 33.3% of bone and soft-tissue cultures, respectively. This rate is lower compared with previous reports in the literature.^{28–30} This may reflect the biopsy technique and that, in this population, most infections would be subacute or chronic in nature. Therefore, the Jamshidi/Trucut biopsy technique is useful to exclude sarcoma but poor at confirming infection. When a positive culture was achieved, *S. aureus* was the most common isolate (as has been reported previously),⁵ followed by acid fast bacilli in keeping with *M. tuberculosis*. Finally, there was a subgroup of cases with negative culture and an inflammatory process described on histology with infection being the most likely cause. These patients were either treated with empirical antibiotics with infection resolution or referred to an alternative service (infectious disease or tuberculosis clinic).

There are several limitations to our study. First, the study population was identified from a single institution, although there were multiple surgeons and teams caring for the patients. Second, our data were collated from retrospective analysis of clinical, biochemical, radiology and histology records, limiting the analysis we could perform. The available data to collect were limited from medical records and may have underestimated the actual incidence of this scenario. In addition, patients were often discharged back to the referring team for definitive management with antibiotics and/or washout. Outcomes of treatment required to resolve infection were thus unable to be accurately quantified.

Conclusion

This study has highlighted the challenges distinguishing bone and soft-tissue infection from sarcoma. Considering the similarities in age, anatomical location and presenting clinical features of infections and tumours, thorough investigation is advocated. As no single clinical, biochemical or radiological feature or investigation can be relied upon for diagnosis, clinicians should have a low threshold for sarcoma multidisciplinary team referral of such cases.

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