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Secondary Sarcomas Associated with Bone Infarct – The Birmingham Experience

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Abstract

The majority of primary bone sarcomas arise de novo, however some develop in association with bone infarction and are only sparsely reported in the literature. The objective of this study was to investigate the 14 cases of secondary sarcoma associated with bone infarct presenting at a single tertiary referral centre at the Royal Orthopaedic Hospital, Birmingham between 1997 and 2019. A retrospective search of our database was carried out for cases of bone infarct-associated sarcomas. The reports of 164 patients with osteonecrosis were retrospectively reviewed. Clinical notes and imaging data were assessed to determine if the underlying bone infarction predisposed the sarcoma. The histological subtype of tumour was determined utilising the WHO classification. Sarcomas and bone infarcts without obvious interconnection, radiotherapy induced osteonecrosis and post-treatment induced tumour necrosis were excluded. 14 patients were identified. Nine cases represented osteosarcoma (64 %) with various differentiations, followed by four cases of chondrosarcoma (29 %). The remaining case was of high grade undifferentiated spindle cell sarcoma, not otherwise specified (NOS). The clinical features (mean age, sex, symptoms, anatomical site, response to treatment and outcome including prognosis) of sarcomas in our cohort correspond to former studies. This is the only study that describes more than ten original cases of secondary sarcomas associated with bone infarct and is the first study to date using the newest diagnostic histopathological criteria in the English-language literature, which allows precise diagnosis of this rare condition.

Keywords: Bone infarct; Osteonecrosis; Secondary sarcoma; Osteosarcoma; Undifferentiated spindle cell sarcoma

Introduction

Origin of secondary sarcoma of the bone can be primary or secondary. Factors leading to the secondary occurrence of this disease can be divided into high-risk (Ollier disease, Maffucci syndrome), moderate-risk (hereditary multiple exostosis, Paget's disease) or low risk (giant cell tumour of the bone, chondroblastoma). The probability of sporadic occurrence of such condition corresponds to moderate or high risk of developing secondary sarcoma and includes mainly radiation [1], osteomyelitis and less frequently rare cases of bone infarcts. The term bone infarcts/infarction describes a condition of osteonecrosis, which can be attributed to a variety of predisposing conditions, such as alcoholism [2], sickle-cell anaemia [3], steroid use [4], decompression sickness (i.e. caisson disease) [5, 6], collagen vascular diseases, rare cases of Gaucher disease [7] and others. [8] However, many patients do not have a defined risk factor for the development of this condition [9]. Bone infarction occurs most commonly in metaphyseal or diaphyseal segments of the long bones. Bone infarcts can also be found throughout in the skeleton labelled as aseptic or avascular necrosis. This can be caused by micro trauma, but remains idiopathic in the majority of cases. Aseptic necrosis is often found during childhood. Osteonecrosis can be initially painful, but most cases are asymptomatic. Although bone infarction is frequently encountered radiologically, the secondary sarcoma arising in association with a pre-existing bone infarct is extremely rare and only sparsely reported in the literature. Most of these are described in case reports or small series only.

The majority of secondary sarcomas arising in bone infarcts tend to occur in the diaphyseal or metaphyseal segments of the long bones, especially in the knee or hip [10], which corresponds with the predominant location of the bone infarct itself. Bone infarct-associated sarcomas mainly occur in patients in the fifth to sixth decade of life with men having a higher incidence. Various histopathological subtypes of such sarcomas have been reported, including malignant fibrous histiocytoma [11,12], osteosarcoma [13], angiosarcoma [14], fibrosarcoma [15], leiomyosarcoma and epithelioid hemangioendothelioma. Malignant fibrous histiocytoma is considered to be the most common type according to the literature. However, this term compromises a whole category of undifferentiated sarcomas, some of which can now be further characterized. Malignant fibrous histiocytoma is now regarded as an obsolete descriptor and the term undifferentiated pleomorphic sarcoma preffered instead. Our study aims to accurately classify secondary sarcomas arising in association with bone infarct. This is based on our cohort of patients and uses up-to-date terminology as well as diagnostic criteria, to specify such neoplasms further histopathologically.

Materials and Methods

We interrogated our oncology databases, which holds clinical and epidemiological data for over 35 000 patients, to identify patients with a diagnosis of bone infarct or bone necrosis. This resulted in a case load of

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164 patients. Clinical and imaging data for these patients were examined to determine whether the underlying osteonecrosis had an association with sarcoma. All non-neoplastic osteonecrosis, radiotherapy induced osteonecrosis, and post-therapy tumour necrosis were excluded. Subsequently, we identified 14 patients with a concomitant diagnosis of the secondary sarcoma arising within a bone infarct. Each diagnosis was confirmed histologically and radiologically. For each patient the sex, age at diagnosis, clinical presentation, anatomical site, histology reports, treatment and oncological outcome were recorded. The histopathological slides of the 14 cases were reviewed and the diagnoses of secondary sarcomas associated with bone infarct were confirmed in all patients. All tissues were paraffin-embedded and stained with haematoxylin and eosin (H&E). Immunohistochemistry (IHC) was performed in three cases. We searched for the microscopic features of the secondary sarcomas. Histological features consisted of an admixture of osteonecrosis along with the morphology of different sarcoma types. These were usually high-grade. From the histopathological point of view the osteonecrosis itself can be divided into early or late stage. Both types were present in our series.

Early osteonecrosis shows bony trabeculae containing empty lacunas devoid of osteocytes, which have undergone necrosis. This is not the only feature as osteocytes may be lost even in normal bone due to decalcification and therefore other signs of infarction are required. These features include ghost marrow cells with pyknotic basophilic nucleated erythroblasts as well as irregular cystic spaces due to fat necrosis in the inter trabecular spaces. Late osteonecrosis is characterized by healing of the necrotic bone identified as non-specific granulation tissue deposition at the periphery of the lesion. The granulation tissue is later replaced by layering of new bone formation with osteoblastic rims on trabecular surfaces. This is known as "creeping substitution". The dead trabeculae are not resorbed by osteoclasts and serve as scaffolds for deposition of new living bone. Focal calcification is also possible in both stages of the bone infarction.

Results

We identified 14 patients diagnosed with secondary sarcoma arising in association with bone infarct. The average age at diagnosis was 49.9 years (range 17-95 years) with six patients diagnosed in the 5th or 6th decade of life. Male to female ratio was 8:6. These demographic characteristics correspond to other published findings. Three patients presented with a pathological fracture and a bone infarct had been radiologically suggestive at the time of diagnosis. One patient had metastases at presentation. In our cohort, 11 sarcomas occurred around the knee, five of them were located in proximal third of tibia and six in the distal femur. One was present in the proximal femur. Two further cases were present in the humerus and one in the pelvis. Thus the majority of the sarcomas in our cohort occurred around the knee, which is a consistent finding according to the literature.In contrast to the published literature where majority of tumours are diagnosed as malignant fibrous histiocytoma, the majority of cases in our cohort were osteosarcomas. The diagnosis of osteosarcoma was reported in nine cases. All of them were considered to be conventional osteosarcoma and were high grade. The differentiation of these osteosarcomas revealed an osteoblastic variant in four cases, a fibroblastic variant in three cases, a chondroblastic variant in one case and the final case was represented a rare variant of giant cell rich osteosarcoma. The second most common histopathological finding was that of chondrosarcoma with four cases. Two of these were low to moderate grade, and two represented dedifferentiated chondrosarcomas. Of these dedifferentiations one had a high grade osteosarcomatous component and the other a high grade spindle cell component. The remaining case was a high grade undifferentiated spindle cell sarcoma, not otherwise specified (NOS).

Treatments varied according to underlying sarcoma type. Seven patients received chemotherapy. Neoadjuvant chemotherapy was given to five patients with the diagnosis of osteosarcoma, and another two patients (also diagnosed with osteosarcoma) received adjuvant chemotherapy. Surgical management included limb salvage in 11 patients (nine endoprosthetic reconstructions, one autograft, and noe curettage with two subsequent excisions) and amputation in two patients. One patient with endoprosthetic reconstruction of proximal tibia developed local recurrence to the thigh with groin lymph node involvement, leading to hip diarticulation one year after the initial diagnosis. Palliative radiotherapy was administrated to one patient at an advanced age, who was diagnosed with undifferentiated spindle cell sarcoma NOS.

Five patients died of their disease (four osteosarcomas, one undifferentiated spindle cell sarcoma). Survival from the time of diagnosis ranged from 11 months to five years. At the time of writing, seven patients (five osteosarcomas, two chondrosarcomas without dedifferentiation) have survived without evidence of disease at 1, 6, 9, 22, 65, 105 and 204 months after the initial diagnosis. The remaining two patients (both dedifferentiated chondrosarcomas) were alive with the disease at the last follow-up, the first had a local recurrence 26 months after the initial diagnosis and the second developed lung metastases at six months after the initial diagnosis. In total four patients (three osteosarcomas, one dedifferentiated chondrosarcoma) developed metastases subsequently, in time period ranging from 4 to 51 months after the initial diagnosis. Metastases occurred most frequently in lungs, but spine and chest wall were also affected in solitary cases. The 2-year continuous disease-free survival in our cohort of patients was 43 % (six of 14 patients).

Discussion

The purpose of our study was to characterize this extremely rare sarcoma type according to up-to-date terminology and diagnostic criteria. The majority of secondary sarcomas arising in bone infarct were formerly labelled as "malignant fibrous histiocytoma" in the literature. However, this histopathological term is now obsolete. It was first introduced in 1961 by Kauffman and Stout and controversy has plagued it since. In 2002, the World Health Organization (WHO) classified this type of tumour as a formal diagnostic entity and renamed it as an undifferentiated pleomorphic sarcoma NOS [13]. This new terminology has been incorporated since then. Other than the pleomorphic variant, there are several other types of undifferentiated sarcomas. These represent a final common pathway in neoplasms that undergo progression towards undifferentiation. These would also include undifferentiated spindle cell sarcoma, which occurred in our cohort in a single case.

Moreover, the features of undifferentiated pleomorphic sarcoma may represent just one section of a tumour. There can potentially be other more characteristic components present which, if biopsied, would lead to a change of diagnosis. This remains a problem of diagnosis and treatment based on small biopsy samples. The biopsied location may not be representative of the underlying tumour or in an area of its highest grade. The process of thorough histological examination of the resection specimen allows a more accurate diagnosis and sub-categorisation. In our cohort, seven cases were initially diagnosed from a biopsy which proved to be representative after examination of the resection specimen and did not result in further categorisation. Six cases were more accurately categorised from the resection specimen or by obtaining more tissue after initial biopsy. One of these cases revealed sarcoma with two different components (dedifferentiated chondrosarcoma with rich osteosarcomatous component). This would not have been discovered if the initial

biopsy was solely used as both components were not present. The next case was initially diagnosed as spindle cell sarcoma, but the resection material revealed osteosarcoma with fibroblastic differentiation. In the last case, three biopsies were required to establish the final diagnosis of dedifferentiated chondrosarcoma with undifferentiated spindle cell sarcoma component.

Another commonly used example of obsolete nomenclature is present in cases diagnosed as "fibrosarcoma". In 1960, Furey reported the first cases of secondary sarcomas arising in bone infarct, both diagnosed as fibrosarcoma. Since then, several other fibro sarcomas with this association were described. However, the diagnostic criteria for this entity have changed significantly over last decade. Currently a large number of fibrosarcoma-like entities can more accurately be identified with modern ancillary techniques such as immunohistochemistry and molecular studies. Furthermore, variable diagnostic criteria historically led to an overlap with the diagnosis undifferentiated pleomorphic sarcoma. Currently fibrosarcoma of bone is a diagnosis of exclusion. It is made after other types of neoplasms are ruled out with immunohistochemistry and molecular studies. This includes tumours with mesenchymal, epithelial, melanocytic, and lymphoid origin. These pose the question as to whether sarcomas previously identified as fibro sarcomas were actually a different entity entirely.

In our study, the most common type of bone infarct-associated sarcoma was osteosarcoma. This histopathological finding differs from the majority of former studies. However, other features of the condition do share similarities with our cases in the literature [15]. These features include age and sex of the patients, anatomical site, clinical manifestation, behaviour of the neoplasm, and response to the treatment. Such sarcomas typically arise about the knee in patients in their 50s-60s with average age of 53.2 years at diagnosis. Men seem to be affected more frequently. A definitive cause of infarction is identified in just over one third of cases and more than 50 % patients die of their disease. The majority of patients who die do so within two years from initial diagnosis. In our series 11 out of 14 cases occurred in the knee region and men were affected more often than women (male to female ratio was 8:6). The mean age of the patients in our cohort was 49.9 years, which is slightly younger than in other studies. In our study, two patients were younger than 25. 36 % (five patients) died of the disease and 80 % (four patients) of them did so within two years from initial diagnosis. This is also a consistent finding according to the literature.

Published literature suggests that chemotherapy prolongs the survival of the patients with sarcomas arising in bone infarct rather, than with surgical management alone [12]. 7 patients in our study received chemotherapy with 2-year disease free survival rate of 57 % (four of seven patients), which is a consistent finding with several studies focusing on the effect of aggressive treatment of sarcomas of bone (including primary, radiation induced, and bone-infarct-associated sarcomas). In comparison, six patients in our cohort were treated with surgery alone and their 2-year disease free survival rate was 33 % (two of 6 patients). One patient was treated with palliative radiotherapy alone because of advanced age. Thus, a combination of any form of chemotherapy combined with surgical treatment seems to have a better outcome and should be considered as a potentially beneficial adjuvant treatment in the management of this disease.

To conclude, our finding mirror that of previous studies in many aspects but where we differ is that the overwhelming majority of our cases were osteosarcomas. We have attempted to account for this as being due to the change in nomenclature and diagnostic labelling which has occurred over the last 20 years. There are several limitations in our study. The cohort of patients is small, a characteristic common to all the studies addressing secondary sarcomas arising in bone infarct due to their rarity. Nevertheless, this is the only study that describes more than ten original cases of secondary sarcomas associated with bone infarct and is the first study to date using the newest diagnostic histopathological criteria in the English-language literature. This was a retrospective study but given the extremely low incidence of this condition it represents the only feasible method of gathering cases. This is reflected in other published retrospective series.

Footnote

Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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