Basic science of musculoskeletal tumours

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Abstract
The basic science of musculoskeletal tumours is a complex subject and has been historically related to pathological descriptions of the lesions. Our understanding of these conditions has increased rapidly with the advent of genetic sequencing and molecular diagnostic techniques. This article covers the main topics and touches on the relevant research strategies which seek to open up further management options, particularly for the sarcomas.

Keywords basic science; musculoskeletal tumours; sarcoma

Introduction
Musculoskeletal tumours encompass a wide variety of entities, and our understanding of them has been historically based on the traditional pathological descriptions of the lesions. These descriptions have evolved into a classification system, of which the World Health Organization (WHO) classification of bone and soft tissue tumours is the essential cornerstone. The histological features of the tumours are now complemented by an array of cytogenetic and molecular diagnostic assays which are increasingly useful for those cases which are equivocal and for further confirmation of a diagnosis. An example of this is cytogenetics to confirm presence of the EWS/FLI1 fusion product in a suspected Ewing’s sarcoma with a histological description of small round blue cells along with immunohistochemical staining that demonstrates high expression of CD99. Another example would be an equivocal case of an active lytic bone lesion that is likely to be benign but with persistent concern that it may actually be a telangiectatic osteosarcoma. The presence of a USP6 rearrangement on cytogenetic testing in such a case would be reassuring that it is an aneurysmal bone cyst, which is a remnant of embryological neuron precursors. Tumours may be secondary due to spread from carcinomas, with bone being the most common site. These metastatic lesions are therefore of epithelial origin, but have a complex interaction with their host site. Haematological conditions can manifest as musculoskeletal tumours, the main ones encountered by the orthopaedic surgeon being myeloma and lymphoma. Finally, syndromic conditions may give rise to widespread musculoskeletal tumours which are often benign but need to be closely observed for malignant transformation.

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Tumours of mesenchymal origin
Musculoskeletal tumours can arise from several main tissue sources. The majority of primary lesions originate from mesenchymal tissue which is analogous to the mesoderm in embryological terms. Neuroectodermal tissue can give rise to primary nerve sheath tumours in the musculoskeletal system and some primary lesions develop from primitive neuroectodermal tissue which is a remnant of embryological neuron precursors. Tumours may be secondary due to spread from carcinomas, with bone being the most common site. These metastatic lesions are therefore of epithelial origin, but have a complex interaction with their host site. Haematological conditions can manifest as musculoskeletal tumours, the main ones encountered by the orthopaedic surgeon being myeloma and lymphoma. Finally, syndromic conditions may give rise to widespread musculoskeletal tumours which are often benign but need to be closely observed for malignant transformation.

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Benign versus malignant tumours
The large number of musculoskeletal tumours is too extensive to list but they can be placed into groups to make initial management decisions easier. Figures 1 and 2 show flow diagrams for benign and malignant tissue tumours respectively.

The diagnosis of benign lesions may be achieved with clinical examination and imaging only, but if there is doubt a biopsy, usually in the clinic may be required for confirmation. Management is then dependent on whether the patient is symptomatic or if the lesion has a risk of malignant transformation then excision may be advised.

The largest group of patients with malignant lesions in the musculoskeletal system consists of those suffering from metastatic carcinoma or myeloma affecting bone. Many of these patients require surgical intervention to prevent an impending pathological fracture or to treat a fracture that has already occurred. It is important to remember that melanoma can metastasize to bone and therefore if there is doubt about the origin of a lesion a biopsy should be performed. The management of bone and soft tissue sarcomas (STS) and metastatic disease has been dealt with in chapters 4 and 5.
Finally, there are some locally aggressive bone lesions with a low risk of metastasizing. These are listed in Table 1. These lesions should be managed by a bone sarcoma centre.

Benign bone tumours

These lesions will be seen by orthopaedic surgeons in a diverse range of subspecialties and can often be dealt with minimal input from an orthopaedic oncology centre. If there is any concern regarding the diagnosis, it is important that the lesion is discussed with the local oncology team and investigations with the appropriate imaging and biopsy performed. Some benign lesions may require excision by an orthopaedic oncologist if the anatomical location would require an extensive approach with mobilization of neurovascular structures (Figure 3). A detailed review of benign bone tumours is provided in the article on Management of benign bone tumours in this issue [http://dx.doi.org/10.1016/j.mporth.2017.03.008].

It is also important to consider that a benign bone lesion may be related to a syndrome, for example multiple hereditary exostosis (EXT gene mutations) or multiple enchondromatosis, the underlying pathophysiology of which is unclear. Such patients need to be monitored closely for malignant transformation in one of their lesions, particularly if it increases in size or becomes painful.

Enchondromas are commonly referred for further evaluation when they are noted incidentally on an MRI scan for joint pain, typically in the distal femur. It is important to re-scan these lesions to assess for change and in some centres dynamic contrast MRI is used to distinguish between enchondroma and grade 1 chondrosarcoma.

Benign soft tissue tumours

There are a huge range of benign soft tissue lesions encountered by the orthopaedic surgeon. Lipomas and ganglia are the most common. Diagnosis should be confirmed by ultrasound and management is based on symptoms. Deep lipomas (subfascial/intramuscular) may reach impressive sizes. MRI is required to exclude areas of dedifferentiation prior to marginal excision. Many of these large deep lipomas will be given a diagnosis of atypical lipomatous tumour (ALT) by the pathologist based on cellular atypia and positive p16 (tumour suppressor protein), MDM2 (tumour promoter protein) and CDK4 (cell cycle regulator) immunostaining. Loss of p16 activity and MDM2 amplification are postulated to be potential events that may lead to the transformation of ALT into liposarcoma.
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