Pathology of soft tissue tumours

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Abstract

Soft tissue tumours are a heterogeneous group of neoplasms with differentiation towards mesenchymal tissue. They may arise anywhere in the body and show similar clinical presentation. Traditional histopathological diagnosis is now complemented by molecular diagnostic techniques that have become firmly established ancillary diagnostic methods. This article provides a short overview of the aetiology and clinical features of soft tissue sarcomas with an update on how molecular genetics is influencing classification and management of these rare tumours.

Keywords Molecular genetics; pathology; soft tissue sarcoma

Introduction

Soft tissue tumours are neoplasms that include a heterogeneous group of diagnostic entities, most of them benign in nature and behaviour. Malignant entities, soft tissue sarcomas, are rare tumours that account for 1% of all malignancies. These are tumours of adults predominantly but 15% arise in children and adolescents. Soft tissue tumours are of mesenchymal origin arising from non-epithelial extraskeletal tissue excluding supportive tissue of viscera, lymphoid and haematopoietic tissue. About 20–30 years ago the diagnosis of soft tissue neoplasms was based on morphological description complemented by a restricted number of special histochemical stains, electron microscopy and, in some cases cytogenetics. Over the last few decades, as in other areas of pathology, the evolution of immunohistochemistry and molecular genetic techniques has had a significant impact on diagnosis and classification of these tumours. The World Health Organization classification of soft tissue tumours (2013)[1] reflects the significance of the application of these ancillary techniques on the diagnosis of soft tissue sarcoma in everyday practice.

Aetiology

The aetiology of most soft tissue tumours is unknown. The large majority arise spontaneously but genetic or environmental contributing factors are sometimes identified. For example, patients with inherited syndromes such as neurofibromatosis, Li–Fraumeni, Gardner or Maffuci show increased susceptibility for development of soft tissue tumours. Kaposi sarcomas frequently arise in states of immunodeficiency. Epstein–Barr virus is associated with the development of a subset of leiomyosarcomas. Irradiation is a recognized risk factor. Patients treated with radiation show increased incidence of angiosarcomas, synovial sarcomas or osteosarcomas developing in the irradiated field. The risk of secondary sarcoma developing correlates directly with the radiation dose. There is no evidence to support the idea that injury predisposes to sarcoma.

Clinical features

The diagnosis of soft tissue tumours is mostly based on clinical information, radiological and histological features (Figure 1). Knowledge of the patient's age and sex, the size and site of tumour as well as family history and past medical history are important for diagnosis. Imaging is pivotal in establishing the tumour location, the type of tissue the tumour originates from and the anatomical relationships of the lesion with adjacent organs or neurovascular bundles. Assessment of the primary lesion is best performed prior to histological sampling to allow for better tumour assessment and to guide the biopsy. Invasion and destruction of surrounding normal structures as well as necrosis are features favouring malignancy that may be identified on imaging. Magnetic resonance imaging (MRI) is, in general, the preferred imaging procedure although computed tomography and ultrasound are also used in the diagnostic pathway.

The majority of soft tissue tumours are benign and present as painless superficial lumps. Sarcomas of the extremities or trunk typically also present as lumps, although their larger size and deep location should alert the clinician. Typically lesions that are superficial and less than 5 cm in maximum diameter are likely to be benign. Lesions deep to the superficial fascia and greater than 5 cm in diameter are more likely to be malignant. Pain and rapid growth are also worrying features in soft tissue tumours.

Some tumours are more common in different age groups. Embryonal and alveolar rhabdomyosarcomas are common in children whilst pleomorphic rhabdomyosarcomas are predominantly seen in adults. Most forms of liposarcomas are extremely rare in children being recognized as almost exclusively an adult cancer. Synovial sarcomas show a peak incidence in young adults. Cutaneous angiosarcomas are most frequent in elderly patients and located in the head and neck region.

Soft tissue sarcomas present late with a mean maximum diameter at diagnosis of 10 cm. This appears to relate to a lack of awareness of the clinical presentation by the patient or clinicians to whom they first present. Current guidelines recommend that any soft tissue lump with any of the following characteristics – greater than 5 cm in size, increasing in size, or deep to the deep fascia should be considered as malignant and referred for further investigation.

Approach to diagnosis of soft tissue tumours

An accurate histological assessment is essential before initiating treatment. Diagnosis of soft tissue sarcoma is predominantly made on a needle biopsy specimen although in some centres fine needle aspiration is used. The advantage of a needle biopsy is that sufficient material is obtained to allow histological assessment of tissue architecture and provides material for immunohistological and, increasingly, molecular studies. It is helpful for

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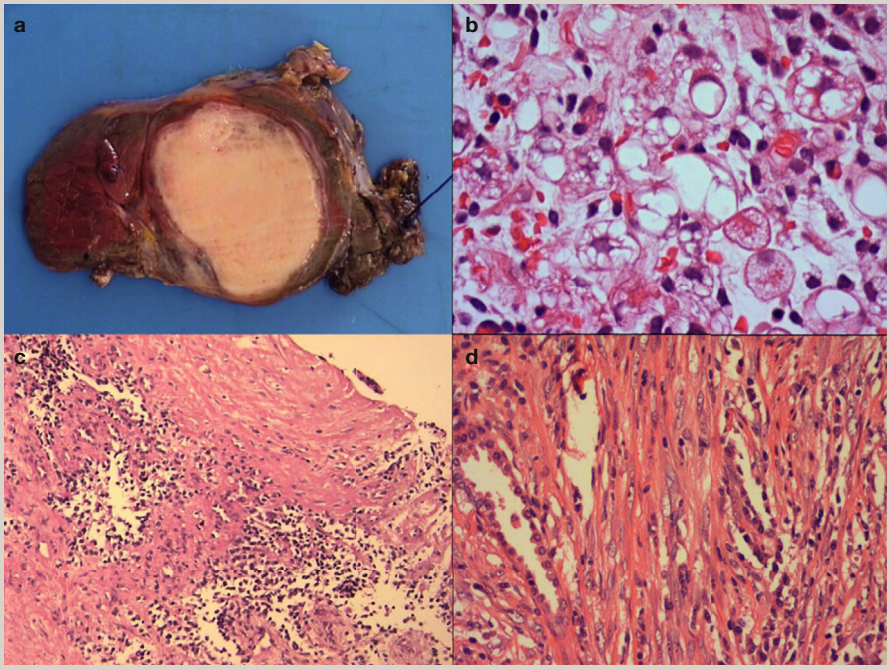

Soft tissue sarcomas are large and deep sited. (**a**) Myxoid liposarcomas contain lipoblasts in a myxoid stroma. (**b**) Alveolar rhabdomyosarcomas typically show central cavitation of tumour nodules. (**c**) Synovial sarcomas have epithelial (often glandular) and spindle cell components (**d**).

Figure 1

the surgeon to discuss the case in advance with the pathologist so that the most appropriate specimen is provided. Submitting fresh tumour tissue in addition to formalin-fixed material allows for cytogenetic analysis. It may be difficult to provide a definitive diagnosis on small samples because of tissue heterogeneity or necrosis. In such instances an open biopsy may be required. This should be obtained by the specialist sarcoma surgeon who is likely to be undertaking the definitive resection as the biopsy tract needs to be removed to prevent local recurrence.[2]

Histological diagnosis of soft tissue tumours is recognized as being one of the most difficult areas in histopathology. There is considerable morphological overlap between soft tissue neoplasms and reactive lesions. Some biologically aggressive sarcomas appear histologically bland whilst reactive conditions such as nodular fasciitis show potentially worrying features including high cellularity and mitotic activity. A wide range of different soft tissue tumours have spindle cell morphology and ancillary stains may be required to show specific differentiation characteristics. Epithelioid morphology is common in sarcomas and this raises the differential diagnosis of metastatic carcinoma or melanoma. In synovial sarcomas true glandular structures can be seen. Soft tissue tumours do not have dysplastic precursors or 'in-situ' components. Instead, they demonstrate features that resemble adult or embryonic tissue of a specific differentiation lineage. Thus, the World Health Organization (WHO) classification groups soft tissue tumours into adipocytic, fibrohistiocytic, smooth muscle, pericytic, skeletal muscle, vascular, chondro-osseous and of uncertain differentiation.[1] Immunohistochemistry is frequently necessary to narrow down the differential diagnosis. However there are a substantial number of tumours in which immunohistochemistry is of limited or no use.[3]

Biological potential and prognostic factors

The current WHO classification of soft tissue tumours recommends separation of soft tissue tumours into four categories: benign, intermediate locally aggressive tumours, intermediate rarely metastasizing and malignant.[4] Benign lesions tend not to recur locally and are often cured by complete excision. Intermediate locally aggressive tumours tend to recur locally if incompletely excised and are locally infiltrative and destructive. They require complete excision with good clearance to avoid recurrences. Intermediate rarely metastasizing tumours are also locally aggressive and metastasis risk is low, less than 2%. Malignant tumours are locally destructive, recur and have a significant potential to metastasize.

Histological grading remains the most important prognostic factor and it is based on histological parameters only.[5] Several grading systems have been published in an attempt to predict clinical outcome. The French system (FNCLCC), currently used in the UK, assesses three parameters: tumour differentiation, mitotic count and tumour necrosis to generate three histological grades (Grades 1–3) by adding scores in each of the different parameters. Grading is useful as it selects patients at risk of developing metastasis; furthermore it helps predict the clinical course and the need for adjuvant therapy. Grading does not have

