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Overview

Advances in the Pathology and Molecular Biology of Sarcomas and the Impact on Treatment

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Abstract

Sarcomas are a complex group of childhood and adult neoplasms with differentiation towards mesenchymal tissues that can occur at almost every anatomic site. Although pathologically diverse, they frequently show similar clinical presentations and radiological findings, such that correct histopathologic diagnosis, utilising the appropriate ancillary immunohistochemical and molecular techniques, underpins their management. This article gives an overview of the pathology, coupled with recent advances in molecular biology, of a selection of soft tissue sarcomas from a clinicopathological perspective, discussing histopathological diagnosis with developments in molecular diagnosis and the incorporation of these findings into diagnostic practice and current and potential targeted treatments.

Key words: Molecular pathology; soft tissue sarcoma; targeted therapy

Statement of Search Strategies Used and Sources of Information

Literature searches were based on PubMed.

Introduction

Sarcomas can arise at any anatomic site as a diverse group of malignant neoplasms with differentiation towards mesenchymal tissues. They account for about 1% of all cancers and 85% arise in adults. Most sarcomas present as enlarging painless masses and because they often show similar clinical and radiological findings, histology (including immunohistochemical and molecular diagnostic modalities) is the definitive diagnostic method. Sarcomas remain mostly aggressive neoplasms with poor prognosis after regional or distant metastatic disease spread. Wide surgical resection and irradiation therapy are the principal therapies for localised disease [1], whereas most patients with metastases require systemic therapy for disease palliation. The options for these patients have been limited; cytotoxic chemotherapy has, for decades, been the predominant treatment for patients with advanced-stage sarcoma. However, many sarcoma subtypes are associated with characteristic genetic abnormalities and our increasing understanding of molecular events associated with each subgroup has led to more sophisticated diagnostic techniques that might indicate specific targeted therapies. This article is an overview of recent advances in a selection of soft tissue neoplasms from a clinicopathological perspective, including molecular developments and their incorporation into practice, and current and potential targeted treatments.

Liposarcoma

Liposarcomas are malignant neoplasms with adipocytic differentiation. There are three main subtypes, the largest of which, well-differentiated liposarcoma (WDL) and dedifferentiated liposarcoma (DDL), represent a morphological spectrum [2]. Histologically, WDL comprises lobules of mature adipocytes intersected by fibrous septa, both of which can display cells with enlarged, hyperchromatic

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atypical nuclei (Figure 1A). WDL does not metastasise but can dedifferentiate into DDL, which is a high-grade undifferentiated pleomorphic sarcoma (Figure 1B) that behaves aggressively. Dedifferentiation is rare in extremity and in superficial soft tissue tumours (termed 'atypical lipomatous tumour'), and is more frequent in the retroperitoneum or mediastinum. WDL and DDL are both associated with high-level amplifications of chromosome 12q14-15, which includes *CDK4* and *MDM2* genes [3–9], and there is also overexpression of the cell cycle regulator p16 (encoded by *cyclin-dependent kinase inhibitor 2A*; *CDKN2A*) [10]. Most WDL and DDL show immunohistochemical expression of CDK4, p16 and MDM2, and this panel of markers is useful in distinguishing WDL and DDL from other adipocytic neoplasms [11,12], whereas fluorescence *in situ* hybridisation for *MDM2* amplification remains the diagnostic gold standard [13–15]. Radical surgical excision is the mainstay of treatment for WDL and DDL. Non-surgical treatment

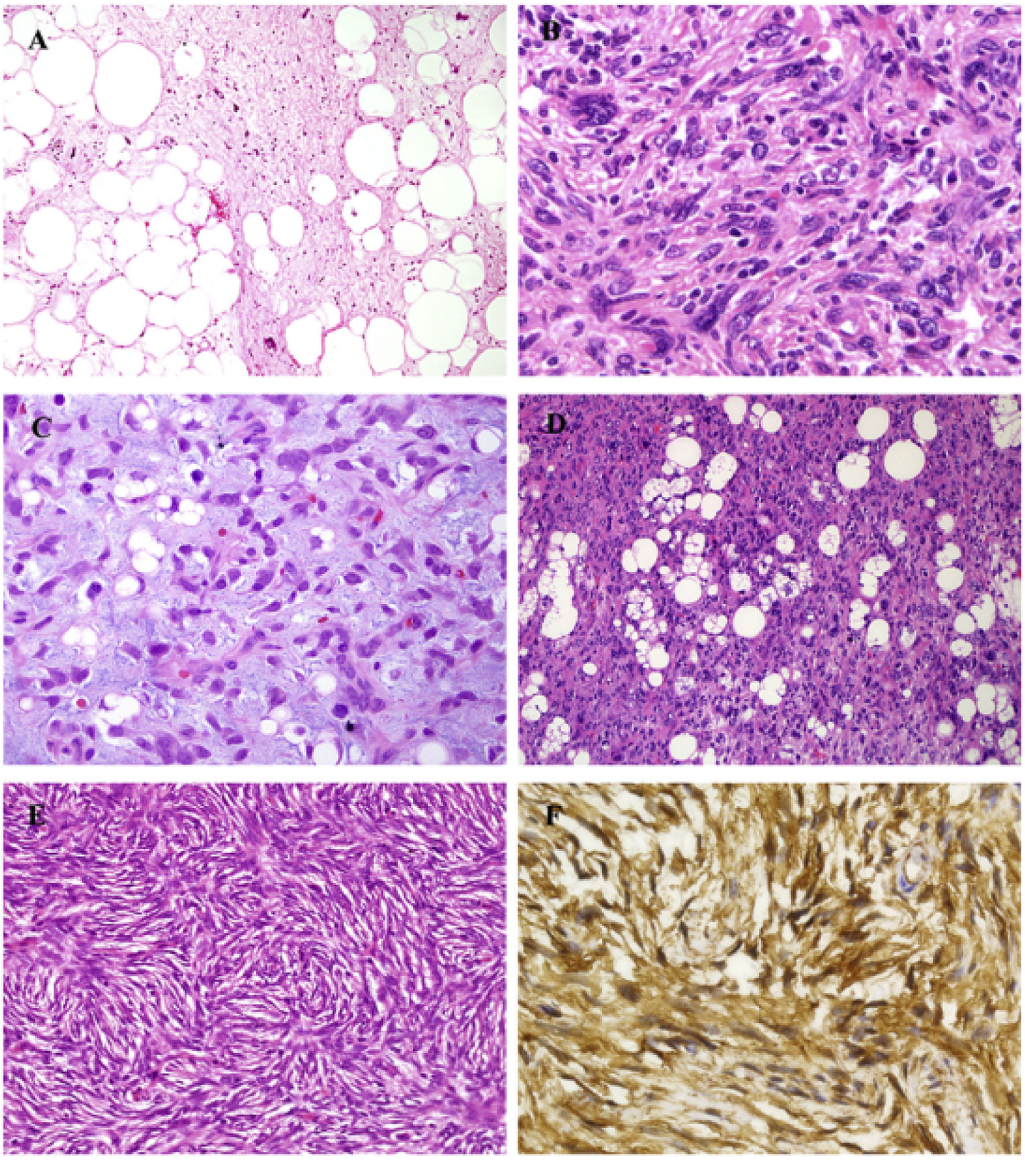

Fig. 1. (A) Well-differentiated liposarcoma. This comprises lobules of mature adipocytes intersected by fibrous septa, both of which can display cells with enlarged, hyperchromatic atypical nuclei. This nuclear enlargement and atypia is usually discernible at low magnification. (B) Dedifferentiated liposarcoma. This represents the more biologically aggressive end of the well-differentiated liposarcoma/dedifferentiated liposarcoma spectrum, and most frequently shows the morphology of a high-grade undifferentiated pleomorphic sarcoma, with sheets of markedly atypical spindle or ovoid cells with hyperchromatic or vesicular nuclei. (C) Myxoid liposarcoma. This is composed of patternless distributions of bland, ovoid cells within abundant myxoid stroma with prominent slender vessels and variable numbers of lipoblasts. (D) Pleomorphic liposarcoma. This neoplasm has the appearance of undifferentiated pleomorphic sarcoma, with markedly atypical spindle and ovoid cells, and interspersed pleomorphic lipoblasts. (E) Dermatofibrosarcoma protuberans. This is the most common dermal sarcoma, and comprises characteristic fascicles of uniform, bland elongated spindle cells in a prominent storiform pattern. (F) Immunohistochemically, dermatofibrosarcoma protuberans is typically diffusely and strongly positive for CD34, a marker which is not specific for this neoplasm but which is expressed by subsets of fibroblasts.

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