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REVIEW

Small round-cell neoplasms of soft tissues: An integrated diagnostic approach

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Summary The family of small round-cell tumours (SRCTs) represents a heterogeneous group of malignancies featuring a primitive, undifferentiated round-cell morphology. SRCTs mostly occur in children, adolescents and young adults, and tend to involve the skeletal system or soft tissue. They constitute approximately 20% of solid tumours in children and, because of their significant morphological overlap, have become a paradigm for an integrated approach to diagnosis. The combination of both immunophenotypic and genetic analysis with classic morphology has proved useful not only on diagnostic grounds, but also in the context of prognostication. This review will focus on SRCTs primarily involving soft tissues and includes the Ewing's family of tumours, also known as Ewing's sarcoma/primitive neuroectodermal tumour, alveolar rhabdomyosarcoma, desmoplastic SRCT, poorly differentiated round-cell synovial sarcoma and mesenchymal chondrosarcoma.

Introduction

The family of small round-cell tumours (SRCTs) represents a heterogeneous group of neoplasms featuring a primitive, undifferentiated round-cell morphology and therefore often lacking any particular morphological features that would allow precise identification. SRCTs occur mostly in children, adolescents and young adults, and tend to involve the skeletal system or soft tissue. They constitute approximately 20% of the solid tumours in children and, when examined by light microscopy alone, often represent a diagnostic challenge.[1] As a consequence, SRCTs have become a paradigm for an integrated approach to diagnosis, one which includes ancillary tools such as immunophenotypic and genetic analysis. The differential diagnosis of SRCTs has become increasingly complex in recent years and continues to be a source of diagnostic uncertainty at a time when specific subtyping is essential for appropriate therapy.

This review will focus on the SRCTs involving primarily the soft tissues and will therefore include the Ewing's family of tumours (EFT), also known as

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Ewing's sarcoma/primitive neuroectodermal tumour (ES/PNET), alveolar rhabdomyosarcoma (ARMS), desmoplastic SRCT (DSRCT), poorly differentiated round-cell synovial sarcoma (PDSS) and mesenchymal chondrosarcoma (MCHS).

Ewing's family of tumours

The relationship between extraosseous Ewing's sarcoma and primitive neuroectodermal tumour (PNET) represents one of the most fascinating controversies in pathology. PNET and Ewing's sarcoma were initially regarded as distinct clinicopathological entities, but it has more recently been argued that they actually represent the same tumour type, diverging only by a higher degree of neural differentiation in PNETs. Numerous studies have shown discrepant results, and it is not yet completely clear whether such a distinction possesses any clinical significance.[2,3] Considering both clinical and morphological evidence along with recent data provided by molecular genetics, Ewing's sarcoma and PNET most likely represent, respectively, the poorly and well-differentiated ends of a spectrum of round-cell sarcomas exhibiting a partial neuroectodermal phenotype, which can be collectively lumped within EFT.

EFTs are rare and account for fewer than 1% of all soft tissue sarcomas. They can present at any age, but the peak incidence is between the first and the third decades. There is no sex predilection, and most cases occur in the deep soft tissues of the paravertebral region and proximal portions of the lower and upper extremities, although visceral locations are being increasingly documented. The involvement of a major nerve that leads to neurological symptoms has been reported in up to one-third of cases, as was the very first example of this entity, described by Arthur Purdy Stout in 1918. Examples of EFTs involving the thoracopulmonary region have acquired the eponym of Askin's tumours.[4]

The gross appearance of these tumours reflects their rapid growth and is usually a large multilobulated soft tissue mass featuring extensive necrosis and/or haemorrhage. In axial tumours, because of osseous involvement, it is frequently difficult to determine whether the origin was in bone or soft tissue.

Histologically, morphology mirrors the degree of neuroectodermal differentiation; most examples of EFT, however, share a predominantly lobular architecture. At the Ewing's sarcoma end of the spectrum, the neoplastic lobules are composed of small round cells exhibiting round or ovoid vesicular nuclei, a distinct nuclear membrane, small nucleoli and poorly defined, scanty cytoplasm (Fig. 1A). At the PNET end, the neoplastic cells may have more abundant, eosinophilic cytoplasm with discernible nucleoli. Importantly, at this better differentiated end of the spectrum, a variable number of rosettes (from scarce to numerous) can be detected (Fig. 1B). Most frequently, the rosettes are of the Homer–Wright type, similar to those seen in neuroblastoma, but Flexner–Wintersteiner rosettes, resembling those present in ependymomas, are occasionally found. Intracytoplasmic glycogen, highlighted by PAS stains, is present in the majority of undifferentiated cases but in only less than half of EFT-containing rosettes. The mitotic activity tends to be quite variable. Necrosis is almost always present and can be extensive, sometimes leaving collars of viable tumour cells around the richly ramified capillary network. EFTs occasionally show atypical cytological features represented by the presence of a focal area containing spindled or large anaplastic tumour cells.

The immunohistochemical profile of EFTs is relatively distinct and plays a major role in the differential diagnosis. CD99 (the product of the MIC2 antigen) represents the most useful marker (Fig. 1C).[5] CD99 represents a cell-surface glycoprotein encoded by the pseudoautosomal *MIC2* gene, which is located on the short arm of the sex chromosomes X and Y. CD99 plays a key role in the differential diagnosis of round-cell sarcomas, as it is preferentially expressed in the vast majority of neoplasms belonging to the EFT group. However, as happens with most immunohistochemical markers, CD99 is not specific. The list of tumours that may express CD99 is very long, but the possibility of diagnostic confusion is in practical terms restricted to a few subtypes of round-cell neoplasm. CD99 is consistently expressed in the majority of synovial sarcomas, in particular when heat-induced epitope retrieval is used.[6] This is particularly important as 20% of synovial sarcomas may exhibit an undifferentiated, round-cell morphology that overlaps morphologically with EFT. Another lesion that can exhibit both morphological and immunophenotypic overlap with EFT is MCHS, most examples of which strongly express CD99.[7] It also has to be emphasised that lymphoblastic lymphomas also express the *MIC2* gene product; but the expression of other lymphoid markers permits the distinction. If CD99 immunopositivity is evaluated in context with morphology and along with the results of the other pertinent differentiation markers, most diagnostic pitfalls will be avoided. Yet there remain cases that may represent a true challenge (Table 1).