What's new in small round blue cell sarcomas?

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Abstract

Establishing a specific diagnosis for a so-called "small round blue cell sarcoma" requires pathologists to consider a broad differential diagnosis and understand the nuanced histology of these tumours. Pathologists must guide the cost effective selection and appropriate interpretation of immunohistochemical and molecular tests in conjunction with histologic and clinical data. We present a review of common small round blue cell sarcomas, highlighting challenging histologic differential diagnoses and diagnostic pitfalls.

Keywords alveolar rhabdomyosarcoma; desmoplastic small round cell tumour; embryonal rhabdomyosarcoma; Ewing sarcoma; immunohistochemical staining; malignant peripheral nerve sheath tumour; synovial sarcoma; Wilms tumour

Introduction

Poorly differentiated small round blue cell sarcomas are challenging to distinguish by histology alone. Accurate diagnosis of these tumours requires pathologists to generate a broad differential diagnosis appropriate to the histology and clinical context. The pathologist must then select distinguishing ancillary studies. The most cost effective route to the correct diagnosis is to identify histologic and clinical clues that narrow the differential diagnosis, and select immunohistochemical and molecular tests to confirm the diagnosis while excluding other reasonable considerations.

We review common small round blue cell sarcomas and their histologic mimics, emphasizing the overlapping histologic, immunohistochemical, and molecular features of Ewing sarcoma, desmoplastic small round cell tumour, Wilms tumour, synovial sarcoma, alveolar rhabdomyosarcoma, and embryonal rhabdomyosarcoma. We highlight distinctive histologic features of these tumours as well as overlapping features and diagnostic pitfalls, with special attention to immunohistochemical and molecular testing.

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Ewing sarcoma

Ewing sarcoma occurs most often in teenagers and young adults. As a bone lesion, Ewing sarcoma has an affinity for the diaphysis of long bones and the ribs. Less commonly, primary tumours can be seen in soft tissue locations or solid organs.[1,2] Cutaneous lesions are especially rare, well-circumscribed, and have excellent outcomes.[3,4]

Ewing sarcoma can show a varied spectrum of histologic features. The histology of Ewing sarcoma is most often characterized by sheets of monotonous cells with round to ovoid nuclei showing finely stippled chromatin. The nuclei are usually separated by a moderate amount of foamy cytoplasm (Figure 1A). Intermixed cells with small, angular nuclei and condensed chromatin can be frequent (arrows in Figure 1). While the nuclear features of Ewing sarcoma are relatively constant, the associated cytoplasm and vasculature can have a variety of appearances. The cytoplasm of Ewing sarcoma can range from relatively abundant and extremely clear (Figure 1B) to scant and densely eosinophilic (Figure 1C). Vessels in Ewing sarcoma are often associated with perivascular spindle cells (Figure 1A); however, thin walled sinusoidal vessels can be prominent (Figure 1C). Ewing sarcoma has a characteristic pattern of CD99 immunohistochemical reactivity with strong, diffuse membranous staining (Figure 1D). Cyclin D1 and NKX2.2 reactivity can also aid in distinguishing Ewing sarcoma.[5,6] Synaptophysin and chromogranin are also frequently reactive, and keratin or S100 reactivity can be seen.[4,7,8]

Pseudorosettes can be frequent in Ewing sarcoma. Historically, tumours outside the central nervous system with numerous pseudorosettes were termed primitive neuroectodermal tumour (PNET). However, these tumours contain identical chromosomal translocations to Ewing sarcoma and are, therefore, regarded as a histologic variant of Ewing sarcoma.

The majority of Ewing sarcomas are characterized by a t(11;22) that results in an *EWSR1-FLI1* fusion gene, seen in 85%–90% of all Ewing sarcomas. *EWSR1-ERG* fusions account for approximately 5% of Ewing sarcoma (Table 1). The remaining cases of Ewing sarcoma, and an emerging family of "Ewing-like sarcomas" contain an expanding family of translocations that may not involve the *EWSR1* gene.[9] These rare variants may represent emerging distinct entities; however these are currently managed clinically as Ewing sarcoma and therefore best considered as related tumours. Notably, *EWSR1* gene rearrangement with various fusion partners is seen in a variety of other histologically diverse tumours, ranging from small round blue cell sarcomas (desmoplastic small round cell sarcoma, clear cell sarcoma) to spindle cell tumours (myoepithelial tumours, angiomatoid fibrous histiocytoma).

The array of clinical and histologic features in Ewing sarcoma can invoke many differential diagnostic considerations. Based on clinical and radiographic features, osteosarcoma is a common differential diagnosis for primary bone tumours, especially when Ewing sarcoma involves the metaphysis. Typically, osteosarcoma

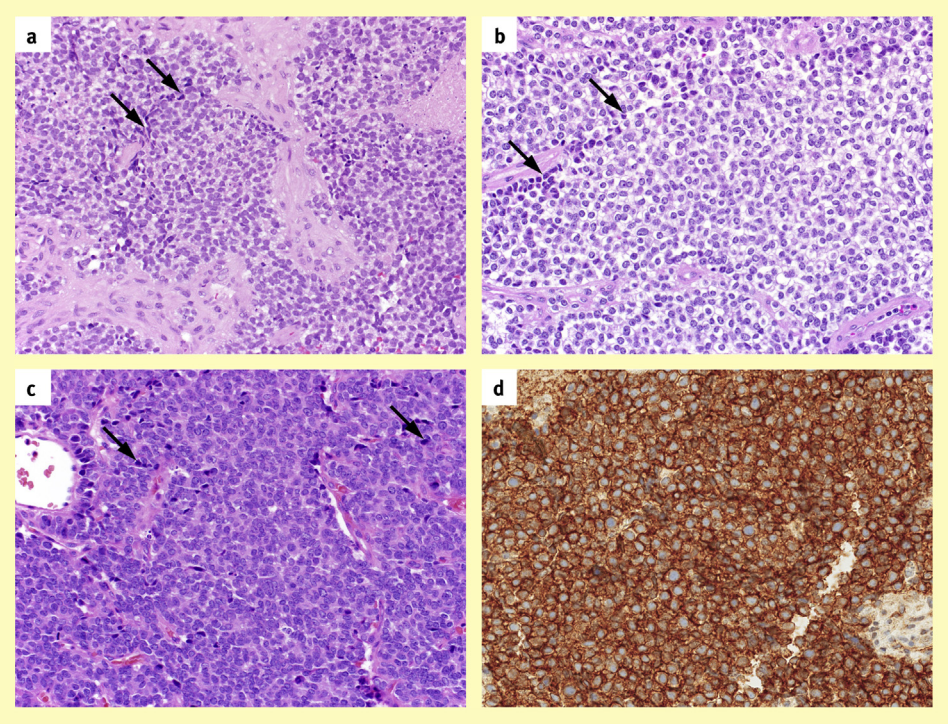

Figure 1 Histolongic and immunohistochemical features of Ewing sarcoma. Ewing sarcoma shows monotonous round nuclei often separated by foamy cytoplasm (**a**, 400× magnification). The cytoplasm of Ewing sarcoma can also range from clear (**b**, 400× magnification) to dense and eosinophilic (**c**, 400× magnification). Smaller cells with condensed chromatin and angular nuclei can be intermixed (arrows in **a**–**c**). CD99 immunohistochemistry nearly always shows strong, diffuse membranous reactivity (**d**, 400× magnification).

is easily distinguished on histologic examination by the presence of nuclear pleomorphism and neoplastic osteoid.

In soft tissue locations, lymphoma, desmoplastic small round cell tumour, alveolar rhabdomyosarcoma and clear cell sarcoma may also be diagnostic considerations based on overlapping histologic features. B-lymphoblastic lymphoma and myeloid sarcoma can show CD99 immunoreactivity identical to Ewing sarcoma. However, lymphomas tend to be discohesive with artifactual separation between cells and single file infiltration into surrounding tissue. Touch preparations from fresh tissue can highlight the discohesive nature of lymphomas. Touch preparations of Ewing sarcoma demonstrate ovoid nuclei, granular cytoplasm, and cohesive groups of cells. Immunohistochemical detection of lymphoid markers (CD45, CD20, CD3 or TdT) can further aid in identifying lymphomas. Since lymphomas frequently manifest with a concurrent leukaemia, examination of the peripheral blood can be informative.

Desmoplastic small round cell tumour has similar cytologic features, and can appear solid without its characteristic desmoplastic stroma. Further, desmoplastic small round cell tumour has identical CD99 reactivity to Ewing sarcoma, and keratin reactivity can be seen in both desmoplastic small round cell tumour and Ewing sarcoma. Features that favour desmoplastic small round cell tumour include dot-like perinuclear desmin reactivity and selective reactivity for the carboxy-terminus of WT1 (no reactivity is seen with the amino-terminus of WT1 in desmoplastic small round cell tumour).[10]

Clear cell sarcoma can also show similar histologic features to Ewing sarcoma, however clear cell sarcoma typically shows small nests of neoplastic cells separated by thin fibrous septae, as opposed to the sheet-like growth of Ewing sarcoma. CD99 reactivity can be similar in both entities. Clear cell sarcoma is distinguished by reactivity for markers of melanocytic differentiation (S100, HMB45, and Melan-A/Mart1), and by a chromosomal translocation that results in an *EWSR1-ATF1* fusion gene.

Alveolar rhabdomyosarcoma can show strikingly similar histologic features to Ewing sarcoma with sheets of monotonous round cells with scant eosinophilic or occasionally foamy cytoplasm. Alveolar rhabdomyosarcoma is easily distinguished by immunohistochemical detection of myogenic markers (desmin, myogenin and MyoD1) and lacks CD99 and Cyclin D1 reactivity.[5] Approximately 80% of alveolar rhabdomyosarcoma contains a *PAX3-FOXO1* or *PAX7-FOXO1* fusion (Table 1).

Desmoplastic small round cell tumour

Desmoplastic small round cell tumour is a rare tumour that most often occurs in males in their teens and twenties. Primary tumours are most often intraabdominal, retroperitoneal or within the pelvis. In many cases, the tumour has spread within the abdomen and studs peritoneal surfaces at the time of diagnosis, resembling carcinomatosis (Figure 2A). As its name implies, desmoplastic stroma is nearly always a prominent feature of desmoplastic small round cell tumour, with small nests of poorly differentiated cells scattered within desmoplasia (Figure 2B). The poorly differentiated component of desmoplastic small round cell tumour shows similar cytologic features to Ewing sarcoma. The nuclei of desmoplastic small round cell tumour are monotonous and round to

