Pathology (■ 2017) ■(■), pp. 1–9

ORIGINAL ARTICLE

Update on molecular findings in rhabdomyosarcoma

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Summary

Rhabdomyosarcoma (RMS) is the most common malignant soft tissue tumour in children and adolescence. Histologically RMS resembles developing fetal striated skeletal muscle. RMS is stratified into different histological subtypes which appear to influence management plans and patients outcome. Importantly, molecular classification of RMS seems to more accurately capture the true biology and clinical course and prognosis of RMS to guide therapeutic decisions. The identification of PAX-FOXO1 fusion status in RMS is one of the most important updates in the risk stratification of RMS. There are several genes close to PAX that are frequently altered including the RAS family, FGFR4, PIK3CA, CTNNB1, FBXW7, and BCOR. As with most paediatric blue round cell tumours and sarcomas, chemotherapy is the key regimen for RMS therapy. Currently there are no direct inhibitors against PAX-FOXO1 fusion oncoproteins and targeting epigenetic cofactors is limited to clinical trials. Failure of therapy in RMS is usually related to drug resistance and metastatic disease. Through this review we have highlighted most of the molecular aspects in RMS and have attempted to correlate with RMS classification, treatment and prognosis.

Key words: Rhabdomyosarcoma; molecular pathology; PAX-FOXO1 fusion; epigenetics; targeted therapy; paediatric sarcoma.

Received 27 July, revised 12 December, accepted 20 December 2016
Available online: xxx

INCIDENCE

Rhabdomyosarcoma (RMS) is the most common malignant soft tissue tumour in childhood and adolescence,[1–7] peaking in children under 4 years of age.[2] It represents approximately 50% of all sarcomas and 4–5% of malignant solid tumours in children aged 0–14 years,[3,4,6] It has an approximate incidence of 4.5 cases per million children per year.[8] Fifty percent of RMS are seen in the first decade of life.[8] However, RMS is exceedingly infrequent in adults. Soft tissue sarcomas make up less than 1% of all adult malignancies and RMS accounts for 3% of all soft tissue sarcomas.[9]

CLINICAL ASSOCIATIONS

Most cases of RMS are sporadic and arise *de novo*. However, certain genetic conditions have been known to be rarely associated with RMS such as Li–Fraumeni syndrome, Beckwith–Wiedemann syndrome, and neurofibromatosis type 1 (NF-1).[10–13] An increased incidence of RMS is noted in genetic syndromes with germ line RAS/MAPK pathway mutations, such as the cardiofaciocutaneous, NF-1, Costello and Noonan syndromes.[14–16] Findings on autopsy reveal that one third of children with RMS have congenital anomalies, suggesting that prenatal events may contribute to tumour development.[17] RMS can occur either as a primary malignancy or as a component of a heterogeneous malignancy, such as a malignant teratomatous tumour.[18]

CLASSIFICATION AND SUBTYPING

RMS stratification into different histological subtypes is important for prognostication and management plans, as RMS are heterogeneous with respect to clinical, morphological, and molecular characteristics, despite sharing the common feature of skeletal muscle differentiation.[2] The World Health Organization (WHO) 2013 classification of RMS subtypes included alveolar RMS (ARMS) including a solid variant, embryonal RMS (ERMS) including botryoid and pleomorphic variants, pleomorphic RMS (PRMS), and sclerosing/spindle cell RMS (SRMS).[19]

The two major histological subtypes of ARMS and ERMS differ in prevalence, site/location, clinical features and outcome.[20]

ERMS represents approximately 70% of all childhood RMS.[1,21] It usually peaks in the 0–4 year age group at approximately 4 cases per 1 million children, with approximately 1.5 cases per 1 million adolescents.[8] ERMS often affects the genitourinary tract and the head and neck regions,[20] especially the orbit. As with most blue round cell tumours of childhood, RMS tends to recapitulate stages of skeletal muscle development in the embryo and fetus. ERMS especially exhibits a broader range of myogenesis and development phenotype that encompasses stellate cells, myoblasts, myotubes and myofibres.[8]

ARMS accounts for about 30% of childhood RMS. ARMS commonly involves adolescents at approximately 1 case per 1 million children.[8] The most common site is the deep tissue of extremities.

Histologically, ARMS characteristically displays an alveolar pattern that is partitioned by thick fibrous septa (Fig. 1A,B). These collagenous septa separate the tumour cells into nests.[8]

ERMS looks at first glance as undifferentiated embryonic mesenchyme (Fig. 2), but further and detailed examination usually shows isolated immature myoblastic cells (Fig. 3).[8] RMS with embryonal histology most closely resembles

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: http://dx.doi.org/10.1016/j.pathol.2016.12.345

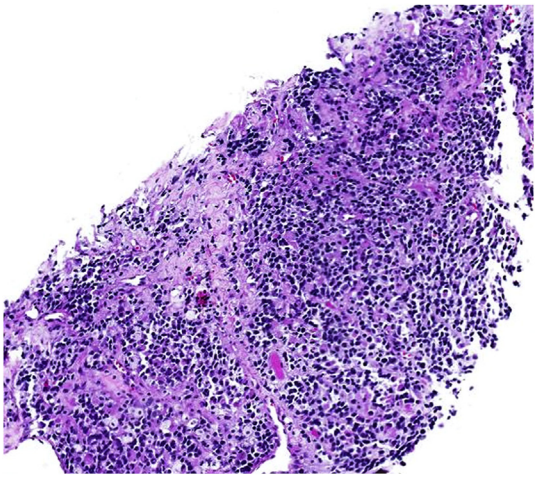

Fig. 1 ARMS characteristically display blue round cells arranged in a pseudoalveolar pattern that is partitioned by thick collagenous septa (H&E; medium power).

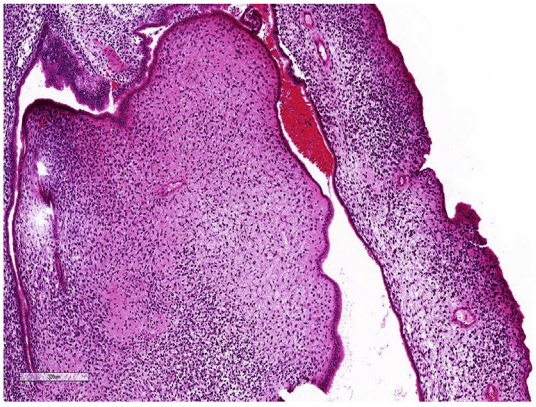

Fig. 2 ERMS with an undifferentiated embryonic ovoid rather than round mesenchyme with subtle hyper-cellularity underlying the luminal surface (cambium layer) (H&E).

muscle of 7–10 weeks gestation, whereas those with alveolar histology resemble muscle of 10–12 weeks gestation.[8]

Although not common, some cases do show a considerable histological overlap between ERMS and ARMS. This may suggest that the two RMS subtypes occur as a result of an arrest at fetal primitive cells inclined towards muscle development/differentiation. The fact that RMS can arise in non-muscular tissue sites also supports this suggestion. In contrast to normal myogenesis, ERMS expresses myogenic regulatory factors such as MYOD1 and MYF5, but they fail to undergo terminal differentiation.[22] MYOD1 has been shown in ERMS cells to retain the ability to bind DNA, but is defective in activating myogenic target genes.[23]

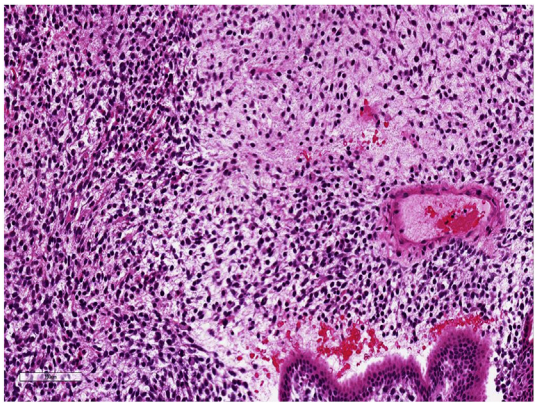

Fig. 3 ERMS with scattered isolated immature myoblastic cells with dense pink cytoplasm (H&E).

Spindle cell/sclerosing RMS mainly arise in the paratesticular region, followed by the head and neck in paediatric populations. As sporadic cases have accumulated in the literature, it has become clear that spindle cell RMS and sclerosing RMS display a significant morphological overlap, which has led to the latest WHO classification scheme where these two subtypes are grouped as spindle cell/sclerosing RMS (SRMS).[24] Sclerosing rhabdomyosarcoma is characterised by a hyalinising, matrix-rich stroma, and pseudovascular growth pattern[25] of spindle cells arranged in an intersecting or herringbone pattern mimicking leiomyosarcoma or fibrosarcoma (Fig. 4A,B). Frequent mitotic figures can be seen.[26] SRMS may show atypical histopathological features of prominent osteoid or chondroid matrix.[27]

Pleomorphic rhabdomyosarcoma (PRMS) is a rare variant of rhabdomyosarcoma, a high-grade neoplasm with skeletal muscle differentiation, that occurs mostly in adults.[28] The

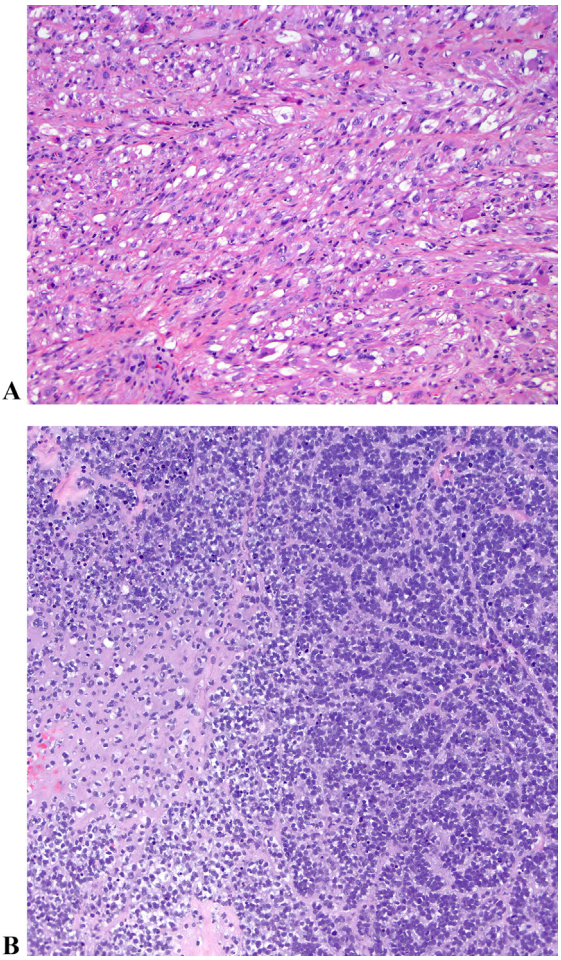

Fig. 4 Spindle/sclerosing RMS exhibiting spindle cells with scattered, polygonal, more differentiated rhabdomyoblasts exhibiting dense eosinophilic cytoplasm (A) and sclerosing RMS with blue round cells traversed by sclerotic collagenous bands (B) (H&E; A, high power; B, medium power). Courtesy of Drs. Miguel Reyes-Múgica and Ranganathan, Sarangarajan.

Please cite this article in press as: El Demellawy D, et al., Update on molecular findings in rhabdomyosarcoma, Pathology (2017), http://dx.doi.org/10.1016/j.pathol.2016.12.345