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SOFT TISSUE PATHOLOGY

Challenging epithelioid mesenchymal neoplasms: mimics and traps

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Summary

Epithelioid mesenchymal malignancies represent a major diagnostic challenge. Epithelioid morphology can be observed in a variety of soft tissue neoplasms, however there exist specific subtypes in which an epithelioid apperance constitutes the most distinctive morphological feature. Moving from epithelioid sarcoma of Enzinger (the prototype of sarcoma with epithelioid morphology), this review will focus on the most relevant entities: namely epithelioid haemangioendothelioma and angiosarcoma, pseudomyogenic haemangioendothelioma, epithelioid malignant peripheral nerve sheath tumour, epithelioid sclerosing fibrosarcoma, epithelioid pleomorphic liposarcoma, alveolar soft part sarcoma, and undifferentiated soft tissue sarcoma with epithelioid morphology. Differential diagnoses and major pitfalls will be discussed in detail.

Key words: Alveolar soft part sarcoma, angiosarcoma, epithelioid malignancies, fibrosarcoma, haemangioendothelioma, immunohistochemistry, liposarcoma, malignant peripheral nerve sheath tumour.

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INTRODUCTION

Epithelioid mesenchymal tumours form a heterogenous group of lesions, at times showing overlapping morphology, and therefore representing a major diagnostic challenge. They also tend to share variable immunophenotypic expression of epithelial differentiation markers (namely cytokeratins and EMA) that, in inexperienced hands, may be a source of further difficulty. Epithelioid sarcomas feature distinctive clinical, morphological, immunophenotypic and genetic findings that will represent the focus of this review. The recently updated World Health Organization (WHO) classification of tumors of soft tissue and bone, has also acknowledged the existence of a subgroup of undifferentiated mesenchymal malignancies characterised by distinctive epithelioid morphology.[1] In general, accurate diagnosis of mesenchymal tumours requires a complex integration of morphological, immunohistochemical, and in selected cases, genetic findings.[2] Such an approach appears to also be extremely effective in this subset of lesions. As already mentioned, there exist several histotype-specific diagnostic pitfalls that will be discussed.

EPITHELIOID SARCOMA

First reported in 1970 by Franz Enzinger, epithelioid sarcoma (ES) is a distinctive sarcoma of uncertain differentiation affecting mainly adolescents and young adults, and showing predominantly epithelioid cytomorphology.[3–5] Two main variants of epithelioid sarcoma have been described: classic-type (C-ES) and proximal type (P-ES).[6] Classic ES occurs in adolescents and young adults (peak incidence being in the second decade) and is characterised by male predominance. It involves mainly the flexor surface of the fingers, hand, wrist, and forearm, followed by knee, lower leg (pretibial region), proximal extremities (buttocks, thigh, shoulder, and arm), ankle, feet and toes. Proximal-type ES occurs in older adults, and tends to involve the deep soft tissue of the trunk, genital areas (pubis, vulva, penis), pelvis, perineum, and head and neck region. The classical type of ES tends to occur distally at onset, propagating proximally along fascial planes, and tendon and nerve sheaths. The recurrence rate (about 80% at 10 years) depends on the adequacy of the first resection. Generally the first recurrence develops within the first year from surgery. The overall recurrence rate reaches 90%, whereas the metastatic rate ranges in different series between 35 and 40%. Metastases involve lung (50%), regional lymph nodes (35%), scalp (20%), bone, and brain. The 10-year overall survival rates vary from 25 to 50%, with recurrences, metastases and death being documented up to 20 years following the initial diagnosis.[7–9]

Morphologically, C-ES shows a characteristic nodular arrangement (Fig. 1A). The nodules are composed of an admixture of eosinophilic epithelioid and spindle cells with variable (from mild to overt) nuclear atypia (Fig. 1B,C). Mitotic activity is usually low. The neoplastic nodules show central necrosis which imparts a pseudogranulomatous appearance, somewhat simulating a rheumatoid nodule or granuloma annulare (Fig. 1D).[10] Necrosis tends to be more abundant in larger and/or deep-seated nodules. Perineurial and perivascular invasion are commonly seen. Nodules can be well-defined or fused into larger masses, forming 'geographic' lesions with scalloped margins. Nodules are generally multiple in recurrences. A pseudoangiomatous pattern (Fig. 1E), calcifications, and bone formation are described. A 'fibroma-like' variant of ES has been reported that is mainly composed of fusiform cells, which most likely represent examples of the recently reported entity 'pseudomyogenic haemangioendothelioma'.[11,12]

Proximal-type ES also shows a multinodular pattern of growth. The nodules are formed by large, epithelioid, carcinoma-like cells with marked cytological atypia, vesicular nuclei and prominent nucleoli (Fig. 1F). The cells are mitotically active and often show a rhabdoid phenotype, characterised by the presence of eosinophilic cytoplasm and eccentric vesicular nuclei with large nucleoli. Interestingly, cases showing hybrid features of both classic and proximal type ES have been observed (Fig. 1G). Similary to C-ES, necrosis tends to be common (Fig. 1H). Immunohistochemically, both variants of ES show co-expression of EMA, cytokeratin (Fig. 1I) and vimentin.[13,14] CD34 immunopositivity is observed in approximately half of cases.[15] Importantly, ES shows loss of nuclear immunoreactivity

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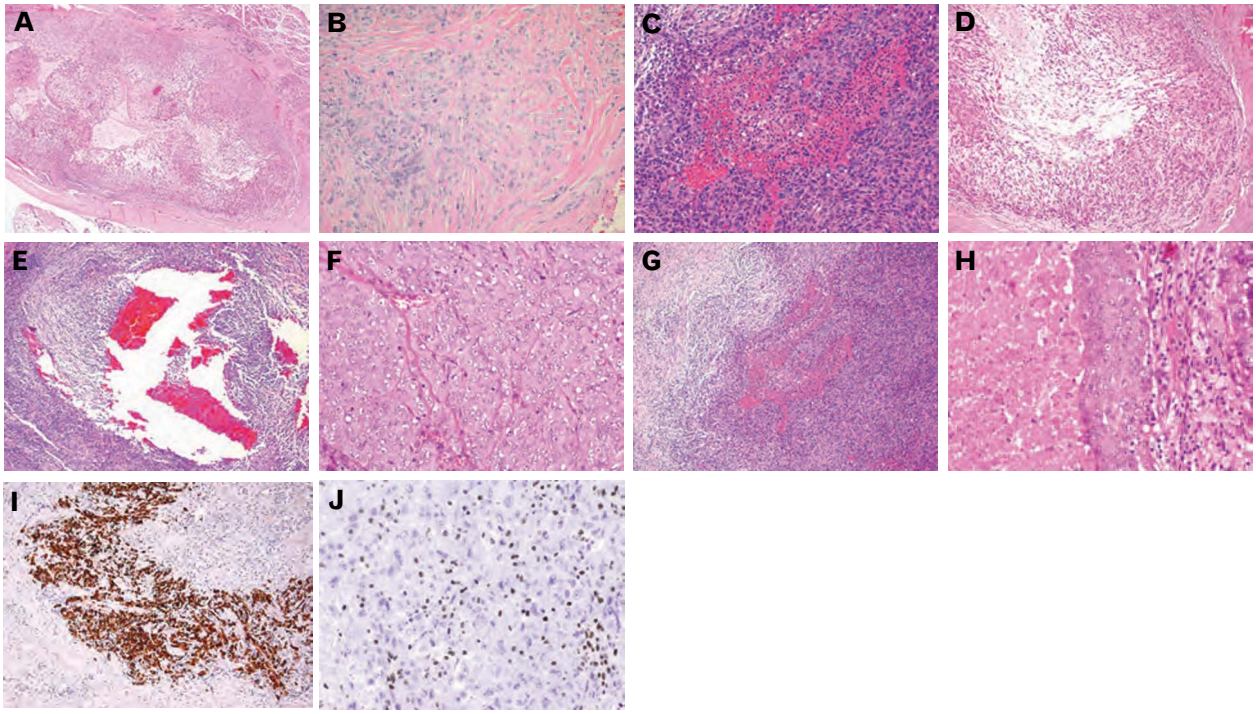

Fig. 1 (A) Classical epithelioid sarcoma (C-ES) at low magnification most often exhibits a nodular arrangement. (B) Cytological atypia may be very mild. (C) In this example of C-ES, severe cytological atypia is seen. (D) Neoplastic nodules of C-ES may exhibit a pseudogranulomatous appearence. (E) Formation of pseudovascular spaces are rarely seen in epithelioid sarcoma. (F) Proximal-type epithelioid sarcoma (P-ES) is characterised by the presence of large epithelioid cells with marked cytological atypia. (G) Rarely, epithelioid sarcoma shows hybrid features of both classic and proximal type. (H) Extensive necrosis is also seen in P-ES. (I) Cytokeratin immunopositivity is almost invariably present in epithelioid sarcoma. (J) Loss of nuclear INI1 expression is an extremely helpful diagnostic clue in epithelioid sarcoma diagnosis.

in the neoplastic cells for INI1[16] (Fig. 1J). This finding represents the epiphenomenon of the inactivation of the *SMARCB1/hSNF5/INI1* gene on chromosome 22.[17–19]

Diagnostic pitfalls in ES diagnosis

Classic-type ES may exhibit a deceptively bland cytomorphology that represents a major diagnostic challenge as well as a potential source of medical litigation: granulomatous lesions (rheumatoid nodule, granuloma annulare) certainly enter the differential diagnosis. Absence of expression of epithelial differentiation markers as well as positive immunoreaction for CD68/CD163 are extremely valuable diagnostic clues. Sarcomatoid squamous cell carcinoma (SSCC) may represent a problem when dealing with elderly patients, however it is exceptional in young adults and adolescents and is consistently CD34 negative/INI1 positive. p63 immunoreactivity is generally observed in SSCC, whereas it is generally negative in ES. More important is the differential diagnosis with myoepithelial carcinoma, which is characterised by a distinctive bimodal pattern of incidence which in approximately 20% of cases involves the paediatic age group.[20] A major pitfall is represented by the fact that myoepithelial carcinoma may also feature loss of INI1 expression.[16] However, they exhibit a more obvious carcinoma-like apperance and, in addition to the expression of epithelial markers, are generally CD34 negative, and variably express S100, GFAP and smooth muscle actin.

P-ES is at risk of being confused with epithelioid vascular malignancies, however it lacks expression of vascular markers, the most useful of which are CD31 and ERG.[21] Malignant rhabdoid tumour (MRT) also shows significant morphological (Fig. 2) as well as immunophenotypic overlap with P-ES (they both co-express EMA and cytokeratin and exhibit loss of nuclear INI1 immunoreactivity). However, MRT mostly occurs in infants and young children, exhibits higher clinical aggressiveness, and shows diffuse rhabdoid morphology. Genetically, MRT exhibits INI1 mutations, which are much rarer in P-ES.

PSEUDOMYOGENIC HAEMANGIOENDOTHELIOMA

In 1992, Mirra and collaborators described four different 'histological pattern subvariants' of epithelioid sarcoma: (1) a granuloma-like variant; (2) an angiosarcoma-like variant; (3) a rhabdoid sarcoma-like variant; (4) a rare fibroma-like variant. This last entity was described as a neoplasm made of a mixture

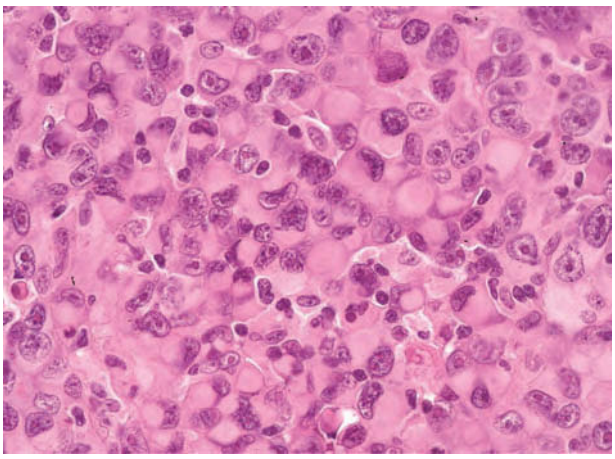

Fig. 2 Malignant rhabdoid tumour typically features large epithelioid cells with intranuclear inclusions representing whorls of intermediate filaments.