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Review article

Updates in keratin-positive mesenchymal neoplasia

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ABSTRACT

Increased access to and utilization of molecular testing in recent years has resulted in rapid discovery of fusion-driven entities in mesenchymal neoplasia. A subset of these rare tumors are defined by cytokeratin expression, which can lead to diagnostic overlap with more common keratin-positive neoplasms (poorly differentiated carcinomas, mesothelioma, etc). Recent examples include spindle cell rhabdomyosarcomas with *TFCP2* fusions, keratin-positive giant-cell rich tumors with *HMGA2::NCOR2* fusions, *NR1D1*- rearranged sarcomas, malignant epithelioid neoplasms with *FET::CREB* fusions, and the very recently described ossifying spindled and epithelioid tumors (OSET). This review will address the unique clinical, histologic, and immunophenotypic characteristics of these rare neoplasms and provide practical considerations for molecular testing in challenging cases of keratin-positive mesenchymal neoplasia.

Introduction

One of the primary goals of a soft tissue pathologist is to exclude sarcomatoid variants of common entities, such as carcinoma and melanoma, which may be amenable to targeted therapy and immunotherapy. This is often accomplished by including a panel of keratins in the work-up of a tumor. Keratins are a diverse group of intermediate filaments that are involved in structure and stability of the cytoskeleton and are enriched in epithelial tissues. Unfortunately, keratins are also expressed in mesenchymal neoplasms. While some sarcomas are definitionally keratin-positive, including synovial sarcoma, desmoplastic small round cell tumor, and epithelioid sarcoma, aberrant keratin expression is a well-known pitfall in smooth muscle and epithelioid vascular neoplasms.

Increased access to and utilization of advanced molecular testing in mesenchymal neoplasia has led to the rapid discovery of new fusion-driven entities, several of which show consistent, often diffuse keratin expression. The aim of this review is to highlight the clinicopathologic characteristics of these emerging entities, with a particular emphasis on distinguishing features that may help guide judicious application of molecular testing to keratin-positive mesenchymal neoplasms (Table 1).

TFCP2- rearranged rhabdomyosarcoma

Rhabdomyosarcomas can be subdivided into embryonal, alveolar, pleomorphic, and spindle cell/sclerosing types. Spindle cell/sclerosing rhabdomyosarcomas include tumors with recurrent molecular alterations including *VGLL2, NCOA2* and *CITED2* rearrangements, as well as *EWSR1/FUS::TFCP2* fusions.[1] In addition to expressing typical markers of skeletal muscle differentiation, *TFCP2*-rearranged rhabdomyosarcomas (*TFCP2*-RMS) are also uniquely distinguished by co-expression of keratin and ALK.

TFCP2-RMS demonstrate a striking predilection for the facial bones including the maxilla, mandible, and skull, although cases have also been reported in the vertebrae, pelvis/chest wall, and femur. While predominantly arising in intraosseous locations, *TFCP2*-RMS may rarely present at cutaneous and soft tissue sites including the trunk,[2–5] bladder,[6] and oral mucosa.[7] Children and young adults are most commonly affected, with more than 50 % of reported cases occurring in patients under 40 years (range 7–86 years; median 31 years).[4,8]

Histologically, *TFCP2*-RMS is characterized by undifferentiated epithelioid to spindled cells with abundant pale eosinophilic cytoplasm and conspicuous nucleoli (Fig. 1A and B). The cells are arranged in sheets and fascicles set within a myxocollagenous and often sclerotic stroma (Fig. 1C). Significant nuclear pleomorphism is uncommon and mitotic activity may be highly variable. Rare cases harbor rhabdomyoblasts.[2,8–10]

By immunohistochemistry, *TFCP2*-RMS is positive for at least one myogenic marker, with MyoD1 expressed most frequently. Myogenin expression, when present, is often limited to rare cells. *TFCP2*-RMS are

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Table 1
Clinicopathologic features that may prompt consideration of molecular testing in keratin-positive mesenchymal neoplasia.

	Clinical presentation	Key histologic features	Ancillary immunohistochemistry	Genetic alteration
TFCP2-rearranged Rhabdomyosarcoma	Facial bones, head and neck region	Mixed epithelioid and spindle cell morphology	Myogenin, MyoD1, ALK	*EWSR1/FUS::TFCP2*
Keratin-Positive Giant Cell-Rich Tumor	Soft tissue: subcutaneous soft tissues of extremities, predominance in young women Bone: long bones, vertebrae	Fibrous pseudo-capsule; peripheral lymphoid aggregates; polymorphous population of mononuclear cells, lymphocytes, foamy macrophages, eosinophilic epithelioid cells (often focal). Prominent evenly spaced giant cells (giant cell-rich variant).	Negative for H3.p35W (G34W)	*HMGA2::NCOR2*
NR1D1-rearranged sarcoma	Subcutaneous soft tissues of extremities, trunk	Multinodular; large epithelioid to polygonal cells with cytoplasmic vacuoles; bizarre multi-nucleated giant cells	Co-expression of S100, ERG, or FOSB in some cases	*NR1D1::MAML1/2/3*
FET::CREB Epithelioid Mesenchymal Tumor	Pleural or abdominal mesothelial-lined surfaces, predominance in children and young adults	Fibrous capsule/septa; admixed lymphoplasmacytic infiltrate; serous microcysts	MUC4 (typically focal) WT-1 positive; other mesothelial markers (CK5/6, D2/40, calretinin) rarely expressed	*EWSR1/ FUS*:: CREB transcription factor family (*ATF1/CREB1/ CREM*)
Ossifying Spindled and Epithelioid Tumor	Soft tissues of extremities, limb girdles	Metaplastic bone shell or fibrous pseudo-capsule; mixed epithelioid and spindle cell morphology	Focal S100 (50 % of cases)	*SRSF7::NFATc3* (50 % of cases)

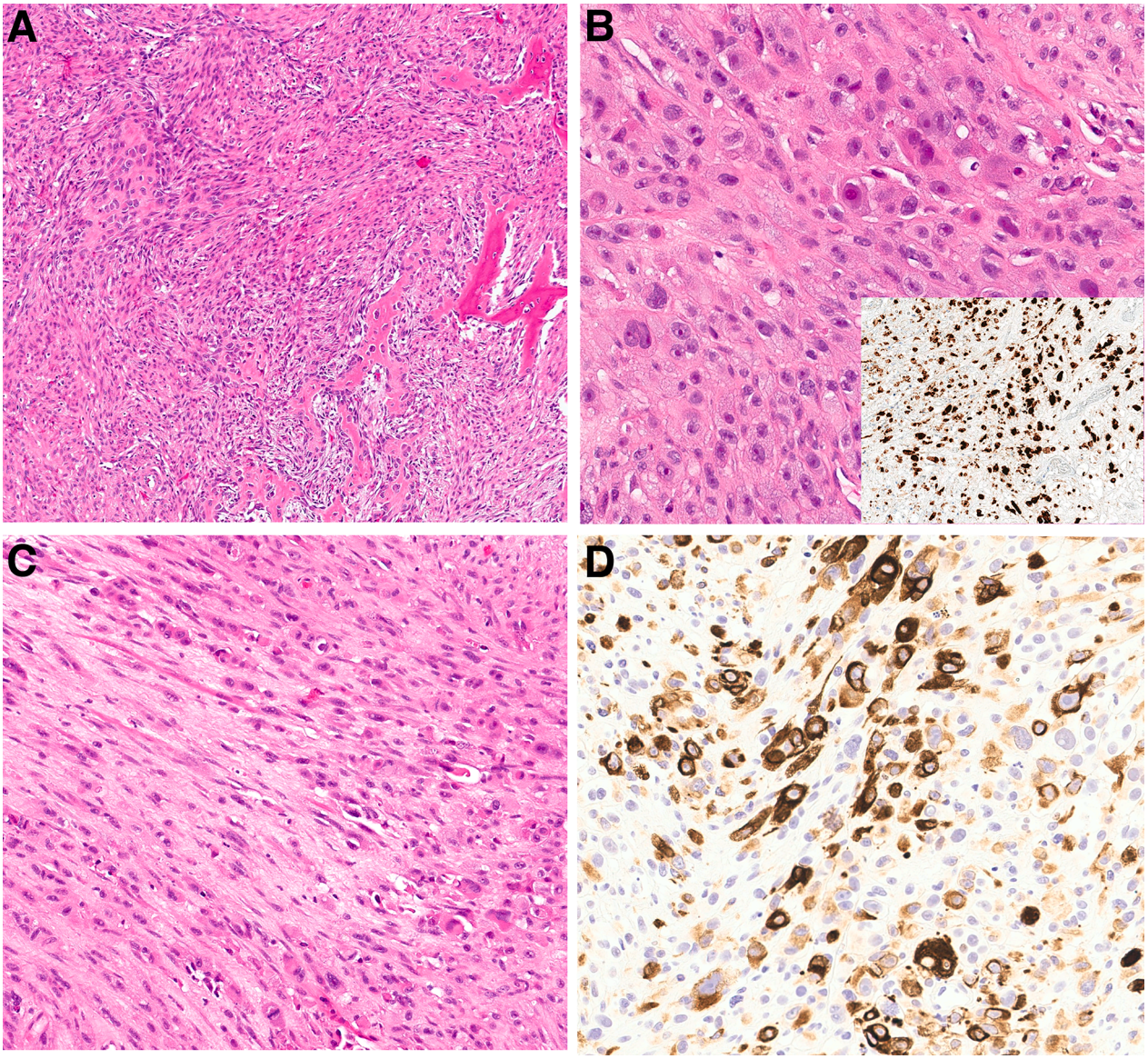

Fig. 1. TFCP2-RMS arising in bone with adjacent reactive-appearing bony trabeculae (A). The cells are epithelioid to spindled and monomorphic with abundant cytoplasm and conspicuous nucleoli (B). Myxocollagenous stroma may be present in some cases (C). TFCP2-RMS frequently co-express cytokeratin AE1/AE3 (D) and ALK (inset B).

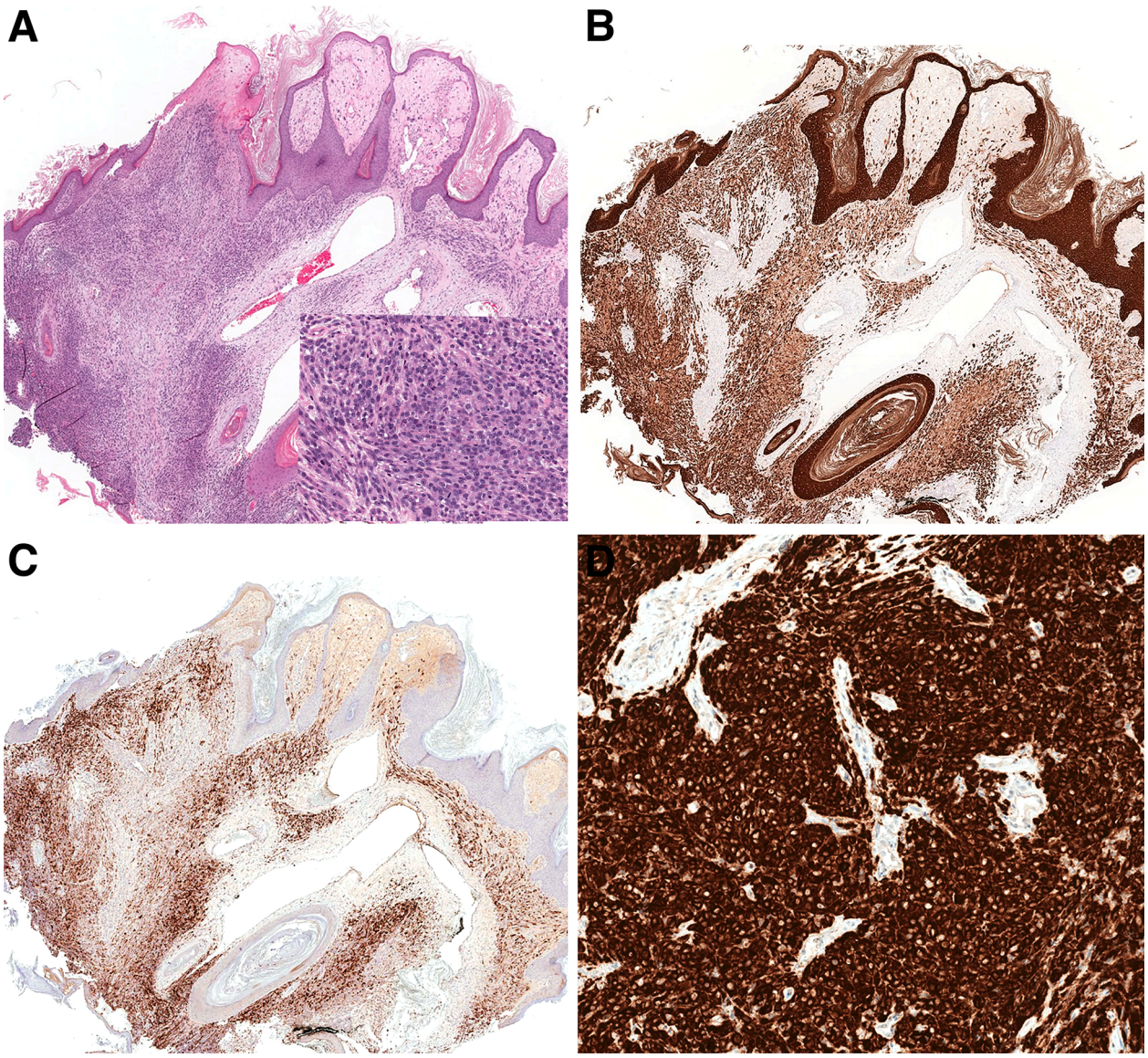

Fig. 2. An example of TFCP2-RMS mimicking sarcomatoid squamous cell carcinoma shows atypical spindled and epithelioid proliferation involving the dermis (A). The overlying epithelium is unremarkable. The spindle cells show expression of cytokeratin AE1/AE3 (B), desmin (C), and ALK (D).

also characterized by keratin expression, which ranges from focal to diffuse (Fig. 1D). Cytokeratin AE1/AE3 and low molecular weight cytokeratins (CAM 5.2, CK7, and CK8/18) are frequently positive with occasional expression of high molecular weight cytokeratins. As noted, *TFCP2*-RMS often expresses cytoplasmic ALK, likely as a downstream effect of ALK upregulation as identified by gene expression profiling (Fig. 1B inset).[11,12] S100 and/or SATB2 may expressed in a small number of cases; SOX10, smooth muscle actin, and caldesmon are typically negative.[8,13,14]

The differential diagnosis for *TFCP2*-RMS is broad. For intraosseous tumors in younger patients, the differential diagnosis includes high grade osteosarcoma. While osteosarcoma may show aberrant keratin or myogenic marker expression, co-expression of these markers is unusual, as is ALK expression. This immunohistochemical panel should be considered in a bone sarcoma lacking significant pleomorphism or arising in a head and neck location. In older adults, intraosseous *TFCP2*-RMS may mimic metastatic sarcomatoid carcinoma. The absence of a visceral primary coupled with co-expression of myogenic markers should prompt consideration of this entity. For cases of *TFCP2*-RMS presenting in superficial soft tissue, especially in the head and neck region of adult patients, sarcomatoid squamous cell carcinoma will often be the primary differential diagnosis (Fig. 2). The lack of epithelial atypia or an in-situ component and/or desmin expression should prompt pursuit of skeletal muscle markers and ALK. Overall, while this unique immunophenotype in the appropriate clinical scenario may be sufficient to suggest the diagnosis of *TFCP2*-RMS, molecular testing should still be pursued in challenging cases or in cases of unclassifiable rhabdomyosarcoma.

Although long-term follow-up data are still limited, initial studies have demonstrated aggressive clinical behavior with frequent local recurrence and distant metastasis, even in the setting of neoadjuvant chemoradiation and resection.[4,8]

Keratin-positive giant cell-rich tumor

Keratin-positive giant cell-rich tumors (KPGCT) with *HMGA2::NCOR2* fusions, also known as xanthogranulomatous epithelial tumors (XGET), are a rare mesenchymal neoplasm originally described by Fritchie et al in the superficial soft tissues and bones of young women.[15] Subsequent studies by Agaimy, Panagopoulos, and Dehner expanded the

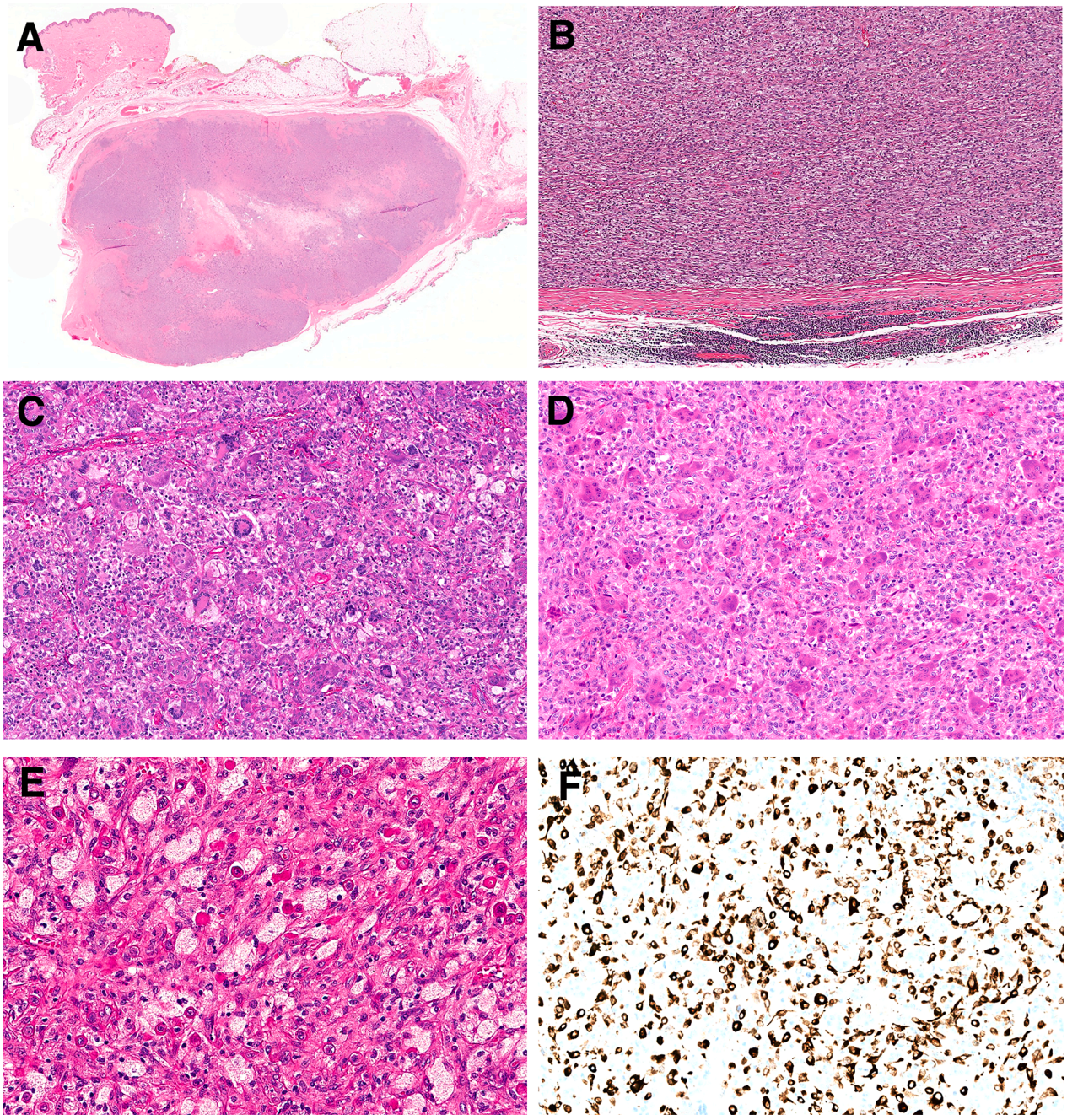

Fig. 3. Soft tissue keratin positive giant cell tumors with HMGA2::NCOR2 fusions often demonstrate a thick fibrous pseudo-capsule with peripheral lymphoid aggregates (A-B). The morphologic spectrum of KPGCT may range from a polymorphous cell population (C) to lesions reminiscent of giant cell tumor of bone (D). Xanthogranulomatous epithelial tumor variant with scattered small brightly eosinophilic epithelioid cells (E). Keratin is at least focally expressed in most cases (F, cytokeratin AE1/AE3).

morphologic spectrum to include a giant cell-rich variant, while also identifying a recurrent unifying *HMGA2::NCOR2* fusion.[16–18] These lesions most commonly affect young adults (range 10 days – 88 years; median 24 years) with a strong female predominance at a broad spectrum of anatomic sites. Most soft tissue-based lesions occur in the subcutaneous tissues of the extremities but have also been reported in the trunk and head/neck regions, including the vocal cord and sinonasal cavity.[19] Osseous lesions are typically found in the long bones and vertebral bodies, and may involve the epiphysis/apophysis. Pelvic and distal extremity tumors have also been reported. When arising in the bone, KPGCTs often present with pathologic fracture and are radiologically described as lytic lesions with peripheral sclerosis. Some lesions demonstrate more aggressive radiologic features including cortical destruction and articular extension.

Histologically, KPGCTs are often multinodular, circumscribed, and surrounded by a dense fibrous capsule with peripheral lymphoid aggregates (Fig. 3A and B). Metaplastic bone formation is uniformly absent. The tumors are composed of a polymorphous population of mononuclear cells with round to ovoid nuclei, foamy macrophages, lymphocytes, and occasional Touton giant cells (Fig. 3C). The giant-cell rich variant also contains prominent evenly distributed osteoclast-type giant cells, reminiscent of giant cell tumor of soft tissue or giant cell tumor of bone (Fig. 3D). A distinct population of epithelioid mononuclear cells with brightly eosinophilic cytoplasm and round nuclei was originally described by Fritchie and colleagues (Fig. 3E); however, these cells may be focal, obscured by surrounding inflammation, or absent.[15]

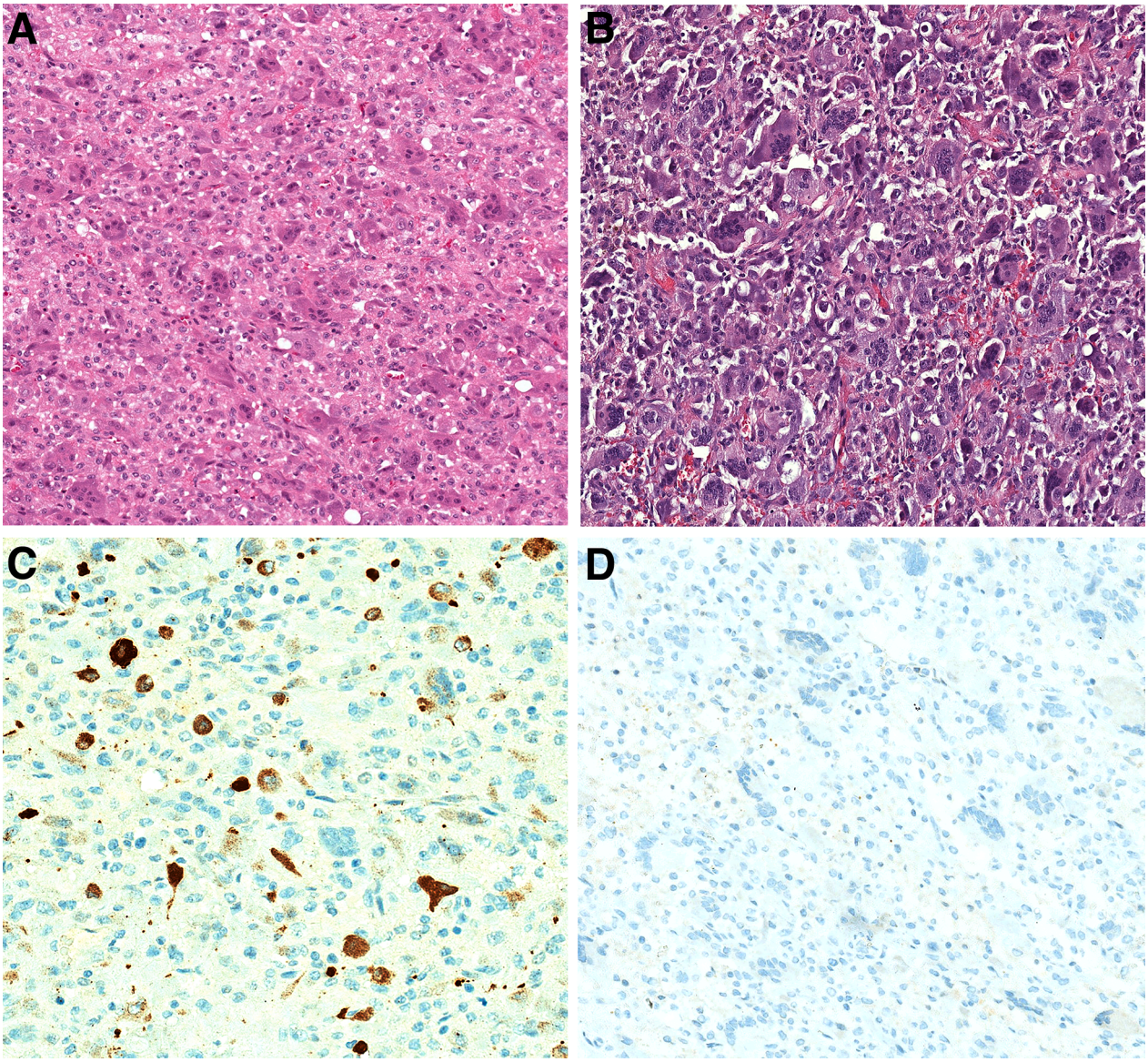

Fig. 4. Histologic sections of a KPGCT with HMGA2::NCOR2 fusion arising in the humerus of a 72 year-old female with a history of breast cancer. This lesion was thought to be a metastasis. Histologic sections show giant cell-poor (A) and giant cell-rich (B) areas. Cytokeratin AE1/3 highlights scattered mononuclear cells raising the possibility of metastatic carcinoma (C), while H3.3 G34W immunohistochemistry is negative (D).

Necrosis, cystic degeneration, and stromal hemorrhage may be seen. Cytologic atypia is absent to mild and mitotic activity is low (< 10 per 10 high power fields).

Immunohistochemically, KPGCT demonstrate consistent but heterogenous expression of broad spectrum and low molecular weight cytokeratin expression that is highlighted in the epithelioid cell population (Fig. 3F). High molecular weight cytokeratin expression (CK5/6) is rarely seen. Histiocytic markers such as CD68 and CD163 may be expressed in associated macrophages. Visceral lineage-specific transcription factors (such as TTF-1, GATA-3, PAX8, etc.), vascular markers, myogenic markers, and SATB2 are negative. BRG1 and INI1 expression are retained. As noted, the majority of KPGCTs have been associated with a novel recurrent *HMGA2::NCOR2* fusion. A case with *HMGA2::COL14A2* fusion has also been recently identified.[20]

The differential diagnosis for soft tissue KPGCT includes other giant cell-rich fibrohistiocytic neoplasms. Tenosynovial giant cell tumors also have a polymorphous cell population that usually includes epithelioid synoviocytes with peripheral hemosiderin granules, which are not seen in KPGCT. Unlike KPGCT, tenosynovial giant cell tumors frequently express clusterin and desmin, but lack expression of keratins. Giant cell tumors of soft tissue and the giant cell-rich variant of KPGCT may demonstrate extensive morphologic overlap. However, giant cell tumors of soft tissue often lack peripheral lymphoid aggregates and demonstrate a partial shell of metaplastic bone in 50 % of cases. A subset of giant cell tumors of soft tissue reportedly express keratin; however, molecular testing was not applied at the time of this study and thus, the relationship between these tumors and KPGCT is unclear.[21] Finally, plexiform fibrohistiocytic tumor is a diagnostic consideration. Although this entity contains giant-cell rich nodules, the nodules are separated by fibrous bands; this lesion also lacks keratin-positive epithelioid cells.

Giant cell-rich KPGCT arising in the bone may be histologically indistinguishable from giant cell tumor of bone. As both may arise at the epiphysis or an epiphyseal equivalent, we would advocate judicious use of keratins and H3.3 pG35W (G34W) immunohistochemistry in this setting. KPGCT with features closer to the XGET end of the spectrum may mimic the solid variant of aneurysmal bone cyst. As aneurysmal bone cysts frequently harbor *USP6* rearrangements, fluorescence in situ hybridization studies for *USP6* or a fusion panel including *USP6* and/or

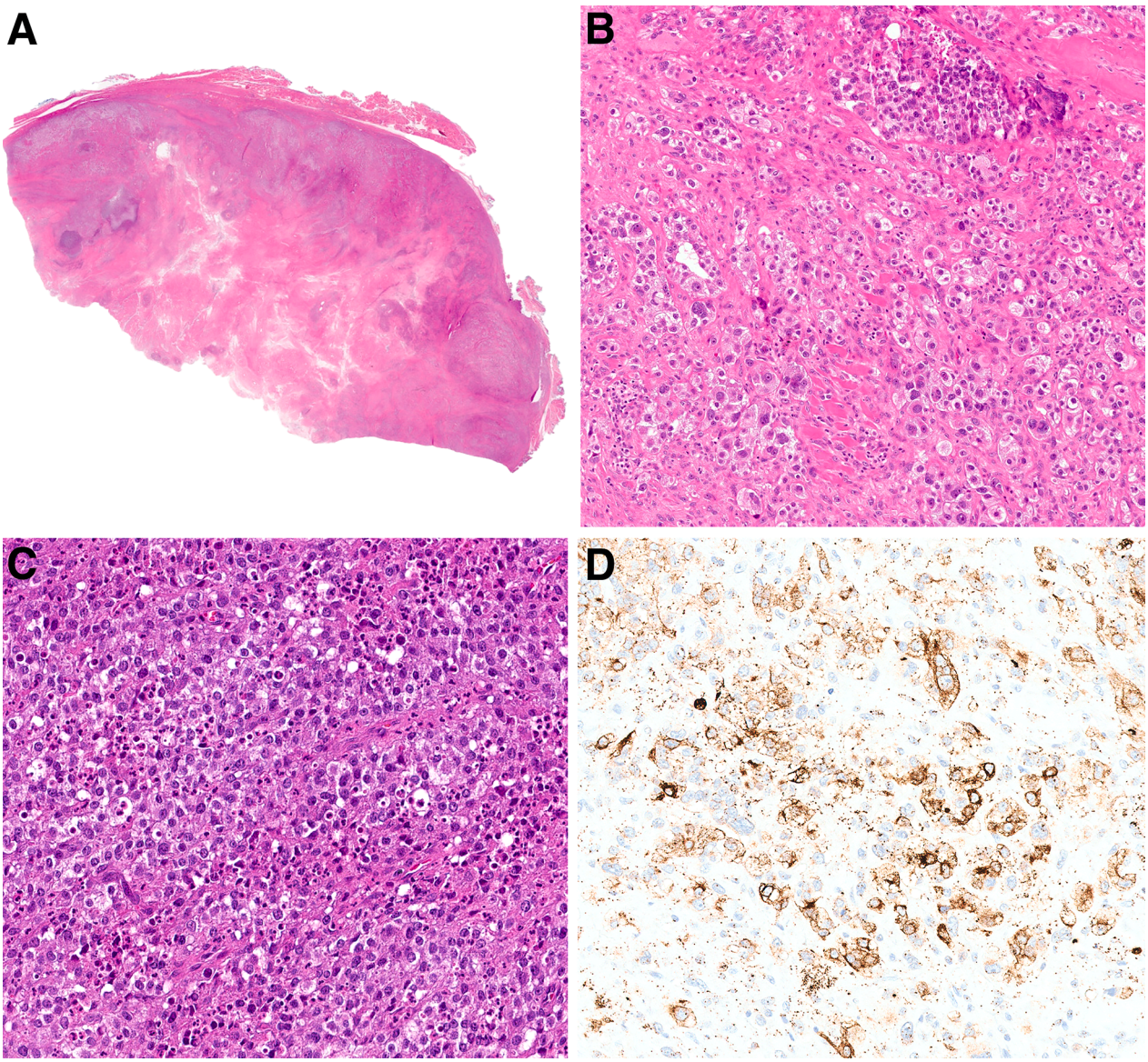

Fig. 5. Low power examination of an NR1D1-rearranged sarcoma with multinodular architecture (A). Characteristic large polygonal cells with eosinophilic to clear cytoplasm (B-C), with bizarre giant cells and pseudo-gland formation (B). Cytokeratin AE1/AE3 expression may be focal or diffuse (D).

HMGA2 genes would be useful in conjunction with keratin staining. Finally, metastatic carcinoma enters the differential diagnosis when KPGCT presents as a bone lesion in an older adult patient (Fig. 4). In this setting, clinical correlation with attention to the presence of a visceral primary may be helpful. Molecular testing interrogating for *HMGA2::NCOR2* may be necessary in patients with a history or concurrent carcinoma.

To date, most KPGCT follow a benign clinical course after surgical excision with clinical follow-up times of up to 14 years.[16] However, local recurrence after incomplete resection has been reported, as well as two cases of metastatic disease.[22] One metastatic case developed in an adult patient with a dorsal metatarsal lesion that metastasized to the soft tissue of the ipsilateral leg 8 months following curettage.[23] The second case arose in the petrous ridge of an infant who developed widely metastatic disease.[24] While surgery is currently the mainstay of treatment, some studies have identified high levels of *CSF1* expression in KPGCT which could provide options for future therapeutic targets in aggressive or unresectable disease.[24–26]

NR1D1-rearranged sarcoma

NR1D1-rearranged sarcoma is a rare soft tissue neoplasm first described by Komatsu et al in the subcutaneous leg in a 10-year-old patient.[27] Subsequent reports and small series highlight a multinodular growth pattern, epithelioid morphology and keratin expression as recurrent features of this lesion, which is now reported in patients of all ages (range 10–85 years; median 41.5 years).[27–32] Complete prognostic information is currently limited by the rarity of this disease; however, initial reports demonstrate the potential for aggressive behavior including local recurrence and frequent metastases to lungs, liver, and bones.

Histologically, *NR1D1*-rearranged sarcomas are often centered in the subcutaneous tissues of the extremities or trunk, but may extend into the dermis, skeletal muscle, or joint space (Fig. 5A). Unusual locations include the tongue and deep central sites, including the iliopsoas.[29,31] The tumor cells are large, polygonal and epithelioid to spindled with eosinophilic to clear cytoplasm and prominent cytoplasmic vacuoles (Fig. 5B and C). Architecturally, the cells are arranged in sheets and nests set in a myxocollagenous stroma with some cases demonstrating

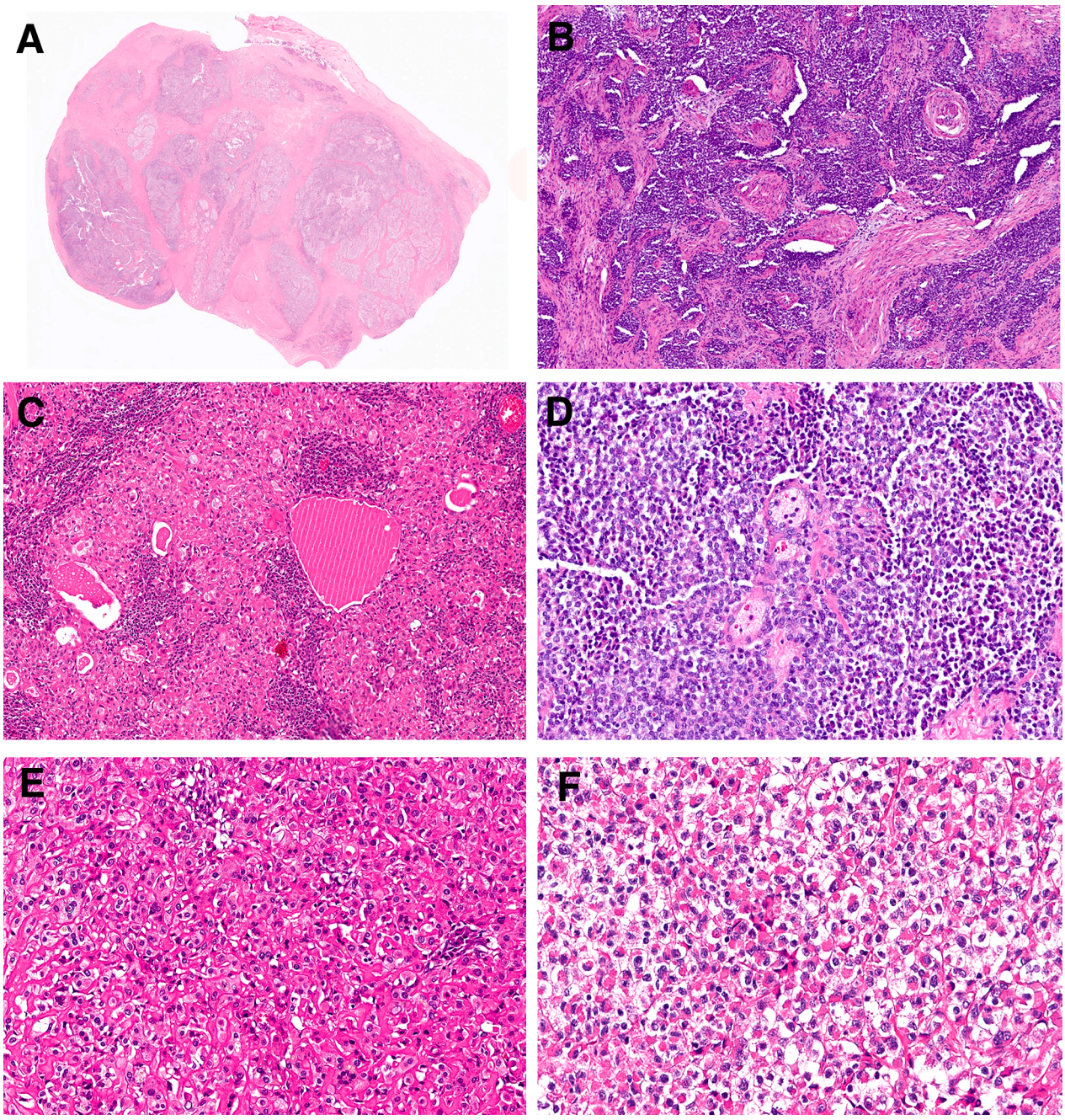

Fig. 6. A. Low power examination of a FET::CREB epithelioid mesenchymal tumor showing encapsulation and nodular appearance (A). A subset shows dense fibrous stroma separating the tumor nodules (B). An example demonstrating brisk admixed lymphoplasmacytic infiltrate and serous microcysts (C). The tumor cells vary from round (D) to epithelioid (E) to rhabdoid (F) in appearance.

cord-like or pseudo-alveolar growth along thin fibrous septa. Bizarre multi-nucleated giant cells (Fig. 5B) and geographic necrosis have been described as recurrent features.[31,32]

By immunohistochemistry, *NR1D1*-rearranged sarcomas are positive for pancytokeratins (cytokeratin AE1/AE3), low-molecular weight cytokeratins (CK7) and EMA, with expression ranging from focal to diffuse (Fig. 5D). High molecular weight cytokeratins, CK20, and claudin-4 are typically negative. A subset of lesions has shown co-expression of ERG and FOSB, as well as S100.[28,30] SOX10, CD34, CD31, myogenic markers, and melanocytic markers are negative, and tumor cells retain expression of BRG1, INI1, and H3K27me3. Next-generation sequencing or FISH studies are required to confirm the presence of an *NR1D1* gene rearrangement (exons 5 or 6), which is usually fused to *MAML1/2/3* (exon 2). Two cases with novel fusion partners have also been reported (*NR1D1::KMT2A, NR1D1::NCOA2*), one of which showed small round blue cell morphology and lacked keratin expression.[31]

The differential diagnosis for *NR1D1*-rearranged sarcomas includes metastatic carcinoma, myoepithelial neoplasms, epithelioid sarcoma and vascular tumors. *NR1D1*-rearranged sarcomas arising in adults at visceral sites may be difficult to distinguish from poorly differentiated carcinoma. Careful examination for a conventional carcinoma component or an in-situ lesion may be helpful. Molecular testing for an *NR1D1* fusion should be explored if the clinical suspicion for a non-epithelial malignancy is high. Myoepithelial neoplasms typically show S100 and SOX10 co-expression. Epithelioid sarcoma should be considered in the

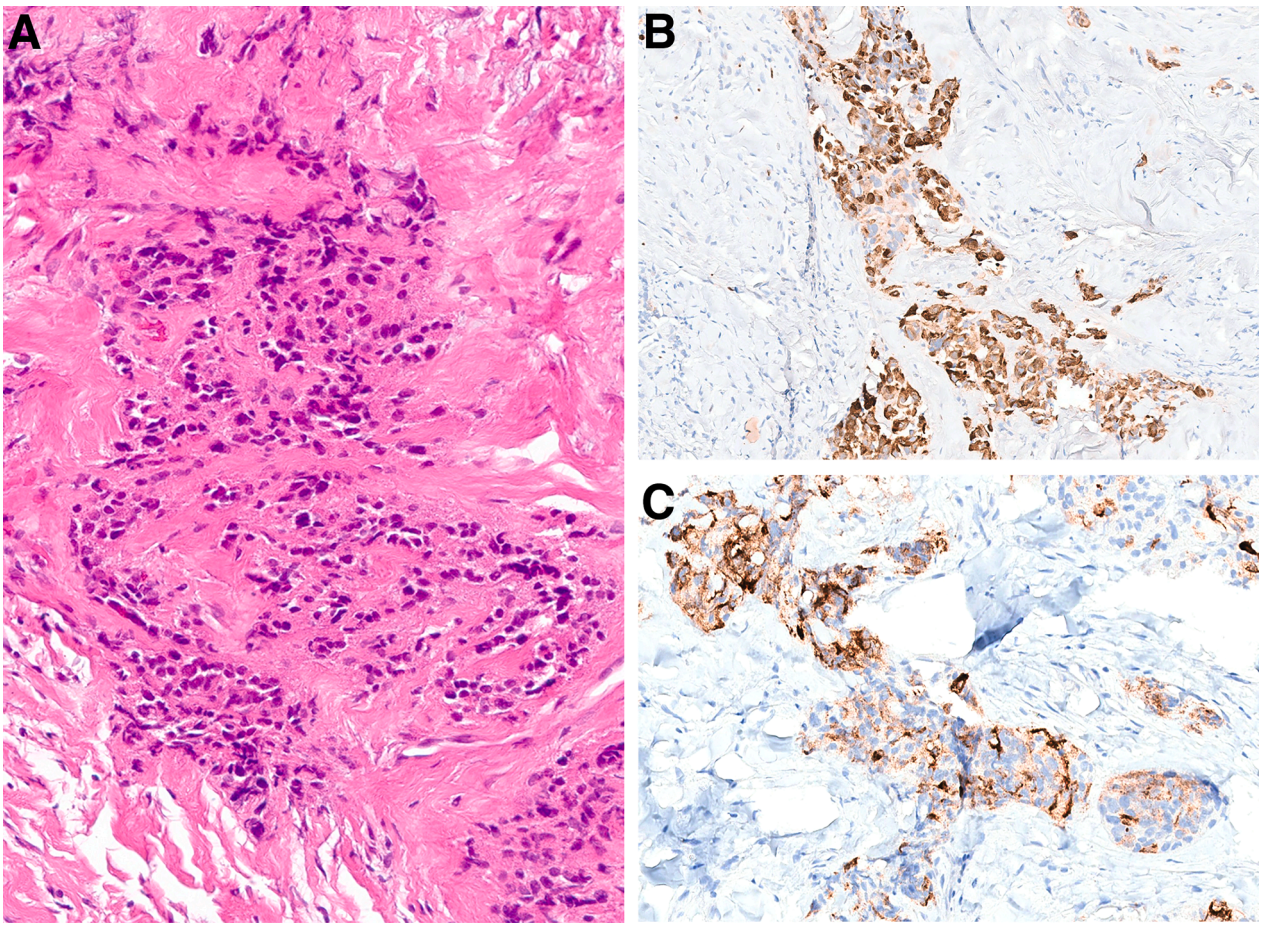

Fig. 7. A case of FET::CREB epithelioid mesenchymal tumor from the chest wall of a 45 year old male mimicking metastatic carcinoma. The tumor cells are epithelioid and nested (A) and show expression of cytokeratin AE1/3 (B) and MUC4 (C). No visceral primary was identified on whole-body imaging.

differential diagnosis of any superficial/subcutaneous keratin-positive epithelioid neoplasm, but retention of INI1 nuclear expression is helpful in excluding this possibility. Finally, the differential diagnosis includes vascular tumors such as epithelioid hemangioendothelioma and angiosarcoma given the presence of intracytoplasmic vacuoles coupled with ERG expression. Lack of CAMTA1 expression and/or CD31/CD34 immunoreactivity would argue against these possibilities.

FET::CREB epithelioid mesenchymal tumor

Fusions between the FET family of RNA-binding proteins (typically *EWSR1* or *FUS*) and the CREB transcription factor family (*ATF1, CREB1* and *CREM*) are present in a diverse clinicopathologic spectrum of mesenchymal neoplasms including clear cell sarcoma, angiomatoid fibrous histiocytoma, malignant gastrointestinal neuroectodermal tumor and primary pulmonary myxoid sarcoma. In 2019, Yoshida et al described two cases of morphologically distinct unclassifiable sarcomas with epithelial marker expression and *EWSR1::CREM* fusions involving the peritoneal cavity and the deep soft tissue of the chest wall.[33] Follow-up studies by Argani et al and others confirmed a predilection for the abdominal and pleural mesothelial-lined surfaces of young patients with tumors frequently seeding the peritoneal cavity, the mesentery, and omental surfaces.[34,35] Visceral and extra-abdominal involvement has also been described including the head/neck,[36] tubal gastrointestinal tract,[34] liver,[37] kidney,[38,39] adnexa[40] and deep somatic soft tissues.[33,41] A significant number of cases occur in children or young adults; however, patients of all ages may be affected (range 6–87 years; median approximately 34 years). Patients frequently present in a systemic inflammatory state with elevated C-reactive protein, anemia, fever, and night sweats. These neoplasms often follow an aggressive clinical course with peritoneal dissemination and metastasis to liver, bone, lung, and regional lymph nodes.

Histologically, *FET::CREB* epithelioid mesenchymal tumors present as solid and cystic masses that are surrounded by a thick fibrous capsule, though infiltration into visceral parenchyma may be seen (Fig. 6A and B). The cells are arranged in sheets, trabeculae, or nests with delicate pericellular collagen, which may occasionally be reminiscent of sclerosing epithelioid fibrosarcoma. Focal papillary or micropapillary architecture has also been described. Other notable characteristics include serous fluid-filled microcysts and a prominent peritumoral or intratumoral lymphocyte population in a subset of cases (Fig. 6C). The tumor cells vary from round/epithelioid to rhabdoid to occasionally spindled with pale eosinophilic to clear cytoplasm and uniform vesicular nuclei (Fig. 6D–F). Nuclear pleomorphism, increased mitotic activity (> 5/10 high power fields), or tumor necrosis may be occasionally present, but are not common features.

By definition, keratin-positive *FET::CREB* mesenchymal neoplasms are essentially always positive for EMA, cytokeratin AE1/AE3 or CAM 5.2, though expression may be focal and/or dot-like. While WT-1 is frequently positive, other mesothelial markers (CK5/6, D2–40, calretinin, HEG-1) are only expressed in a small subset of cases. Rare cases have also demonstrated loss of BAP1 nuclear expression. Claudin-4 and visceral organ lineage-specific transcription factors (TTF-1, PAX8, CDX2, GATA-3, etc) are negative which is helpful in distinguishing these lesions from carcinoma. Synaptophysin is frequently positive and may rarely exist with chromogranin co-expression, prompting consideration of a well-differentiated neuroendocrine neoplasm in non-somatic soft tissue sites.[36,39,40] MUC4 and cytoplasmic ALK are often focally

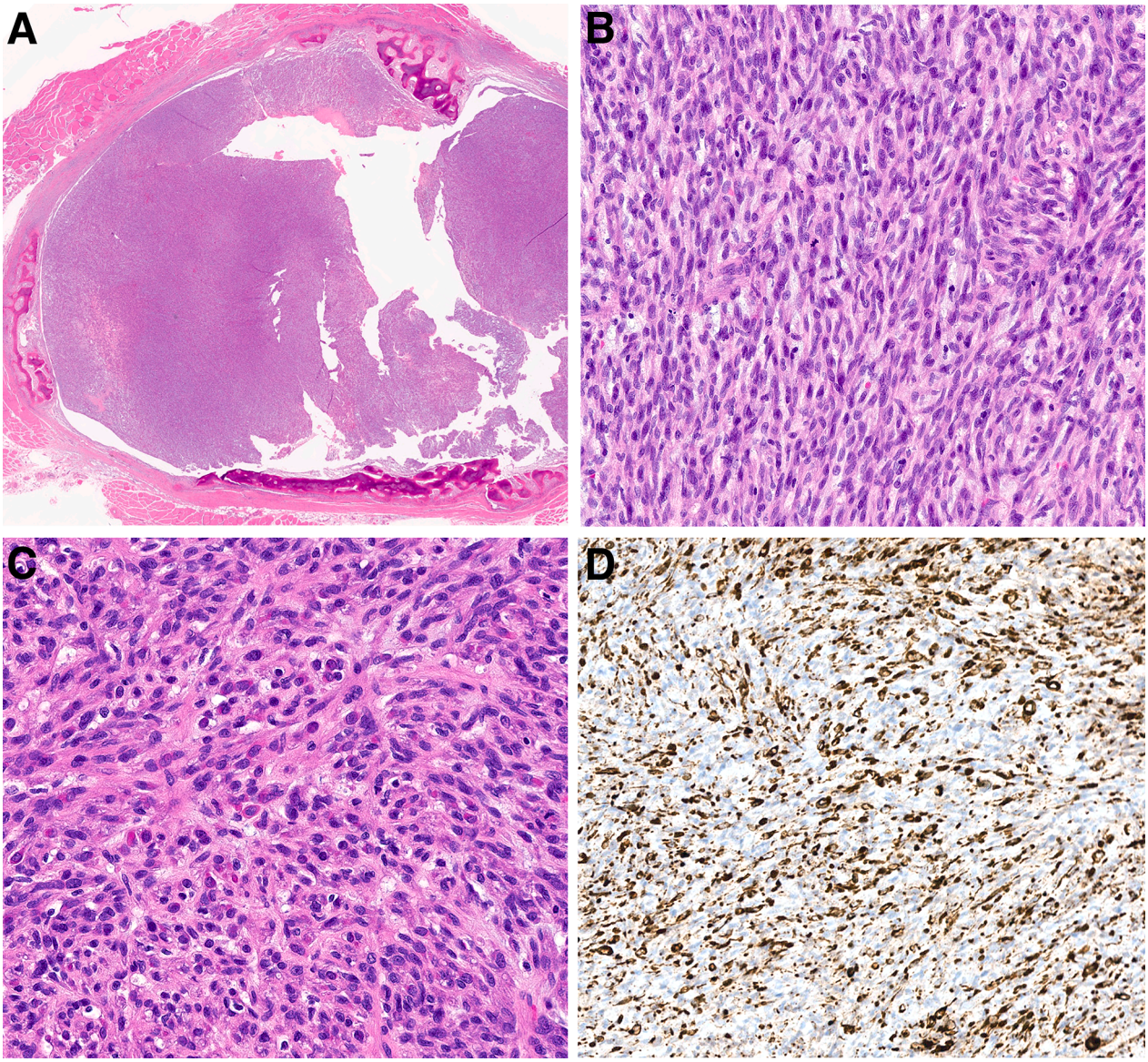

Fig. 8. Ossifying spindled and epithelioid tumors (OSET) frequently demonstrate a fibrous pseudo-capsule and partial rim of metaplastic bone (A). Spindled cells with a myoid cytomorphology (B) and a minor epithelioid component (C). Cytokeratin AE1/AE3 may be expressed in both components (D).

expressed while S100, SOX10, and melanocytic markers are negative. H3K27me3, BRG1 and INI1 are retained.

Given the anatomic location of most *FET::CREB* epithelioid mesenchymal tumors, mesothelioma and carcinoma are primary considerations, confounded by the presence of consistent epithelial marker expression. Unlike many mesotheliomas, most *FET::CREB* epithelioid mesenchymal tumors are negative for calretinin and lack BAP1 loss or *CDKN2A* homozygous deletion. However, the involvement of mesothelial-lined spaces, occasional papillary architecture, and frequent co-expression of other mesothelioma markers raises the possibility of phenotypic overlap. The relationship between *FET::CREB* lesions and other fusion-driven mesothelial neoplasms, including those with *EWSR1::YY1* rearrangements, also remains poorly understood.[35,42] *FET::CREB* epithelioid mesenchymal tumors may also mimic primary or metastatic carcinoma, especially in cases that co-express MUC4 (Fig. 7). The age of the patient, uniformity of the tumor cells, and low mitotic rate argue against carcinoma. In ambiguous cases, fusion testing is recommended.

Tumors that express MUC4 may cause diagnostic confusion with sclerosing epithelioid fibrosarcoma. MUC4 expression seen in the *FET::CREB* neoplasms is typically focal compared to diffuse expression in the latter, while keratin staining would favor *FET::CREB* epithelioid mesenchymal tumors. Next-generation sequencing studies are usually conclusive for morphologically ambiguous cases, as most sclerosing epithelioid fibrosarcoma are characterized by fusions between either *EWSR1* or *FUS* and *CREB3L1/2*.

Ossifying spindled and epithelioid tumor (OSET)

Ossifying spindled and epithelioid tumor (OSET) is an emerging entity recently described by Gross et al in a series of 12 cases.[43] Affected patients are typically in their late teens to late 30 s (range 12–58 years, median 32.5 years) and often present with a mass that has been present for several years. To date, cases have arisen in the soft tissues of the extremities and limb girdles. The lesions are well-circumscribed and surrounded by a shell of metaplastic bone or dense fibrous pseudocapsule (Fig. 8A). True to its name, OSETs are histologically characterized by fascicles of plump uniform spindled cells with a myoid cytomorphology that are juxtaposed with a minor component of eosinophilic epithelioid cells (Fig. 8B and C). Nuclear pleomorphism, atypical mitotic

figures, or tumor necrosis are notably absent.

Immunohistochemically, OSET is positive for cytokeratin AE1/AE3, low molecular weight cytokeratins (CK7, CAM 5.2, and CK 8/18) and high molecular weight cytokeratins (namely CK5/6). Keratin expression is often confined to the epithelioid cells, though the spindle cell component may also occasionally show expression (Fig. 8D). Regarding other broad-spectrum epithelial markers, EMA is frequently positive while claudin-4 is negative (n = 2 cases). Approximately 50 % of cases demonstrate rare S100 expression, and a small subset focally co-express SATB2. SOX10, MUC4, ALK, and markers of myogenic or vascular differentiation have been negative in all tested cases, and tumor cells retain expression of BRG1, INI1, and H3K37me3. Whole transcriptome sequencing studies and fluorescence in situ hybridization studies (FISH) have identified a recurrent *SRSF7::NFATc3* fusion in approximately 50 % of OSET cases. Regrettably, these genes are not currently available on most targeted RNA-based fusion panels (Archer, TruSight, etc).

OSET shares several radiologic and histologic features with ossifying fibromyxoid tumor including a multinodular architecture, peripheral shell of bone, and focal expression of S100 protein. Like OSET, ossifying fibromyxoid tumor may also occasionally express cytokeratins.[44,45] However, ossifying fibromyxoid tumor demonstrates an ovoid cytomorphology and fibromyxoid stroma that are not characteristic of OSET, as well as frequent expression of desmin and recurrent *PHF1* fusions. Myositis ossificans may also be considered in the radiologic differential diagnosis given the peripheral shell of bone. Unlike OSET, the spindle cells in MO are positive for smooth muscle actin, negative for keratins, and frequently demonstrate *USP6* rearrangements. When considering other keratin-positive neoplasms, the histologic differential diagnosis includes pseudomyogenic hemangioendothelioma given the shared myoid cytomorphology and keratin expression. However, pseudomyogenic hemangioendothelioma also expresses vascular markers and is genetically characterized by *FOSB* rearrangements. Synovial sarcoma and epithelioid sarcoma are also in the differential diagnosis but can be excluded with SS18-SSX or INI1 immunohistochemistry, respectively.

At present, OSET appears to follow a benign clinical course with no reports of recurrence or metastasis in 11 patients following surgical excision (follow-up time 5–240 months, mean 42.6 months). Both time and the identification of additional cases will be critical in expanding the clinicopathologic spectrum of these unusual lesions.

Conclusion

Increased access and utilization of molecular testing in the diagnosis of mesenchymal neoplasms has led to the discovery of several new fusion-driven entities that, by definition, express keratins. Careful correlation with clinical features and ancillary immunohistochemistry and molecular testing is critical. It must be emphasized that a diagnosis of a rare "zebra" tumor should only be pursued following judicious exclusion of other common keratin-positive neoplasms, particularly in tumors arising in bone or visceral organs. However, interrogation for these novel mesenchymal tumors should be entertained in a keratin-positive neoplasm presenting in a child/young adult or in an adult without a visceral primary.

CRediT authorship contribution statement

Alexandra L. Isaacson: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **Karen J. Fritchie:** Conceptualization, Data curation, Formal analysis, Writing – review & editing.

Declaration of competing interest

Both authors, Alexandra L. Isaacson and Karen J. Fritchie, declare no financial or personal conflicts of interest related to the contents of this article.

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