Rib destruction by epithelioid tumour in a young man

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CLINICAL QUESTION:

A man in his 30s presented with back pain and was found to have a tumour in the posterior chest wall. Imaging showed an expansile mass measuring up to 6.7 cm, centred on the left posterior 11th rib with diffuse cortical destruction. The tumour displaced the left hemidiaphragm, and was in contact with the spleen, with no infiltration seen. There was no involvement of the overlying skin. PET-CT showed the lesion to be inhomogeneously hypermetabolic, with a mainly peripheral distribution of FDG. Staging imaging showed no other abnormality. The patient was otherwise well with no medical history and no significant family history. A CT-guided biopsy was performed. Review the high-quality, interactive digital Aperio slide at http://virtualacp.com/JCPCases/jclinpath-2019-206338/ and consider your diagnosis.

WHAT IS YOUR DIAGNOSIS?

A. Metastatic carcinoma.
B. Alveolar rhabdomyosarcoma (ARMS).
C. Sclerosing epithelioid fibrosarcoma (SEF).
D. Spindle cell/sclerosing rhabdomyosarcoma.
E. Osteosarcoma.
F. Ossifying fibromyxoid tumour (OFMT).

DISCUSSION

This is a tumour composed of relatively uniform, minimally to mildly pleomorphic, medium-sized cells with round to ovoid nuclei and clear to lightly eosinophilic cytoplasm. The cells are present in groups, nests and occasionally individually, within densely fibrous stroma, with areas suspicious of osteoid formation.

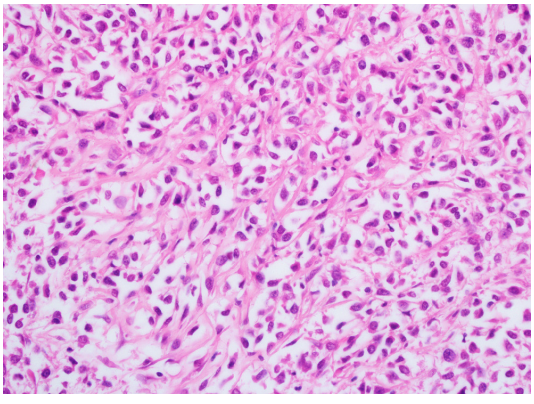

Figure 1 Sclerosing epithelioid fibrosarcoma. The tumour is composed of nested distributions of relatively uniform epithelioid cells, with ovoid nuclei and abundant clear cytoplasm. The epithelioid morphology mimics the appearance of more common neoplasms, especially carcinoma.

In this case the tumour is diffusely and strongly positive for MUC4 and CD99, and focally for CD57. This particular case is negative for AE1/AE3, Cam5.2, CK7, TTF1, desmin, smooth muscle actin (SMA), myogenin, FLI1, neuron-specific enolase, CD56, synaptophysin, chromogranin, glial fibrillary acidic protein, TLE1, CD45 and CD138. There is a normal staining pattern for p53, and INI expression is retained in nuclei. Fluorescence in situ hybridisation with break-apart probes flanking *EWSR1* or *FUS* genes showed separated *EWSR1* signals, and a normal *FUS* signal pattern. The features are consistent with SEF.

ARMS typically has a markedly nested pattern, with prominent central dyscohesion and necrosis, often with thick surrounding fibrovascular septa. The cells of spindle cell/sclerosing rhabdomyosarcoma typically have deeply eosinophilic cytoplasm, sometimes with cross striations and can have extensive extracellular stroma.[1] Both forms of rhabdomyosarcoma can contain rhabdomyoblasts, and immunohistochemistry is positive for desmin and myogenic transcription factors myogenin and MyoD1. ARMS has characteristic translocations involving the *FOXO1* gene with either *PAX3* or *PAX7*.[2 3] Some cases of intraosseous spindle cell/sclerosing rhabdomyosarcoma harbour translocations involving *FUS* and *EWSR1*, but these have not been shown to partner *CREB3L1* or *CREB3L2* seen in SEF.[1 4 5] Carcinomas display varied morphology, but usually show more atypia and lack thickened fibrous septa. Some SEF can show focal epithelial membrane antigen (EMA) expression, but they usually lack the strong and diffuse cytokeratin expression of most carcinomas. Although MUC4 is expressed in most SEF, this can be expressed by carcinomas, so is not a distinguishing feature. OFMT is composed of uniform, small rounded cells and these may be in nested patterns with surrounding fibrous septa, reminiscent of SEF. However, OFMT is associated with peripheral mature bone, present as a surrounding rim, or sometimes as tongues dividing the cellular nests, in contrast to SEF. Unlike osteosarcoma, SEF is typically composed of cells with more uniform nuclei and scanty cytoplasm, lacks lace-like bone deposition and strong uniform immunoreactivity for SATB2, while exhibiting MUC4 positivity which is absent in osteosarcomas.[6]

SEF is a rare neoplasm, usually affecting adults (average age 40–50 years) with no clear gender predominance.[7 8] It usually arises in the deep soft tissue of limbs, limb girdles, trunk or neck,[7 8] although more rarely can arise in visceral sites or bone.[6 8–10] SEF is an aggressive tumour which is prone to persistent or recurrent disease (50%–57%) and metastasis (43%–86%, including to bone, and metastasis needs

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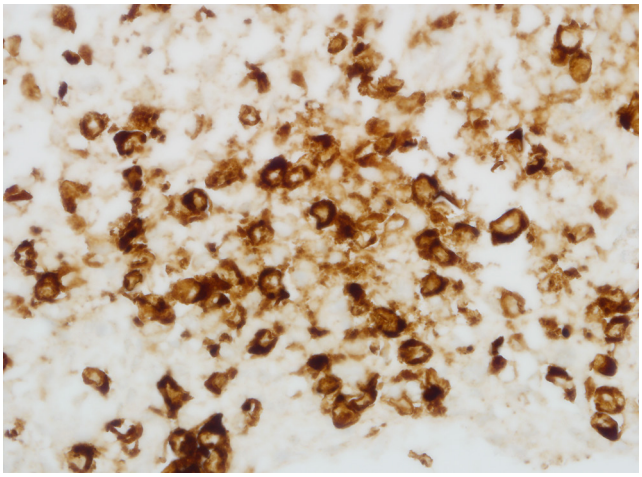

Figure 2 Sclerosing epithelioid fibrosarcoma (SEF). Immunohistochemistry for MUC4 shows strong expression of this marker within the tumour. This is a relatively sensitive marker for SEF, helping to distinguish it from other sarcomas, although it can also be expressed in carcinomas.

exclusion before a diagnosis of primary SEF of bone).[6 8 9 11 12] Macroscopically, SEF is usually circumscribed, firm, pale and multinodular, sometimes with cystic spaces or areas of calcification.[8 9] Microscopically the tumour has a dense hyalinised to sclerosed stroma, separating nests and cords of tumour cells (figure 1).[8 9] The deeply eosinophilic collagen may appear reminiscent of delicate osteoid.[8] The cells are relatively uniform and polygonal with ovoid to angulated or folded nuclei with small amounts of clear cytoplasm.[8 9] Dyscohesion between cells can give an alveolar appearance.[8] Occasional features include focal haemangiopericytoma-like vessels and necrosis.[8 9] Focal osteochondroid differentiation and metaplasia may occur.[8] There may be areas of fibrosarcomatous pattern and the tumour has been described with other patterns of fibrosarcoma, for example, low-grade fibromyxoid sarcoma (LGFMS) (with which there is genetic and clinical overlap), conventional fibrosarcoma or low-grade myxofibrosarcoma.[8 9]

The immunoprofile of SEF is variable and non-specific. While most SEF are positive for bcl-2 and around half express EMA focally (42%–50%), they are less frequently positive for AE1/AE3 and Cam5.2 (0%–14%) and S100 protein (0%–29%), and only focally.[7–9] MUC4 is positive in 78% of SEF (figure 2) and in all hybrid LGFMS-SEF tumours.[7] Most pure SEF harbour rearrangements of the *EWSR1* gene, most frequently with *EWSR1-CREB3L1* fusions and more rarely *EWSR1-CREB3L2*. Fusions involving the *EWSR1* gene are more frequent than those involving *FUS*. Rearrangement of the latter gene is more frequently present in LGFMS; cases of LGFMS which progressed to SEF and cases with hybrid features are associated with *FUS-CREB3L2* or *FUS-CREB3L1*.[4 6 13–16] Rare cases have been described with other translocations, including *PAX5-CREB3L1*, *FUS-CREM* and *EWSR1-CREB3L3*.[17–19]

Data on therapy options are limited due to disease rarity. While surgery, radiotherapy and chemotherapy have all been employed, one study showed long-term survival only with microscopically clear resection margins.[20]

Take home messages

- Sclerosing epithelioid fibrosarcoma (SEF) is a rare type of sarcoma, and its diagnosis may be missed because of its morphological and immunophenotypic overlap with other neoplasms.
- The most frequent sites of occurrence are the deep soft tissues of limbs, limb girdles, trunk and neck.
- The morphology is of relatively uniform, polygonal cells with ovoid nuclei and small amount of cytoplasm, with nests, groups or files of cells separated by densely hyalinised stroma. Haemangiopericytic vessels, necrosis and osteochondroid metaplasia and/or differentiation are occasionally seen.
- Most SEF show strong expression of MUC4, although the immunoprofile is otherwise non-specific, and can overlap with neoplasms in the differential diagnosis such as carcinomas.
- SEF is predominantly associated with rearrangements of the *EWSR1* gene, with *EWSR1-CREB3L1* fusions or more rarely *EWSR1-CREB3L2* gene fusions.
- Despite the relative morphologic uniformity and lack of marked atypia, SEF is an aggressive tumour with frequent locally persistent or recurrent disease (50%–57%) and metastasis (43%–86%).

ANSWER

C. Sclerosing epithelioid fibrosarcoma (SEF)

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