Evidence of nerve sheath differentiation and high grade morphology in sclerosing epithelioid fibrosarcoma

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Abstract

Sclerosing epithelioid fibrosarcoma is a recently described sarcoma in which ultrastructural evidence of fibroblastic differentiation forms part of the diagnostic criteria. This report describes a further case of this tumour, which showed evidence of both fibroblastic and perineurial differentiation by immunohistochemistry and electron microscopy, and which had areas of high grade morphology. The tumour metastasised and the patient died of disease 12 months after presentation. The relevance of these findings to diagnosis and differentiation in these tumours is discussed.

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Since publication of the first series of 25 cases of this distinctive rare variant of fibrosarcoma in 1995,¹ a further eight cases, including a single cytogenetic study, have been reported.²⁻⁵ The importance of ultrastructural examination in supporting a diagnosis made on morphological and immunohistochemical criteria has recently been highlighted.³ We describe a further case of sclerosing epithelioid fibrosarcoma in which focal, histologically atypical areas were accompanied by immunohistochemical and ultrastructural features suggestive of nerve sheath, in particular perineurial, differentiation, and discuss the relevance of these findings with respect to diagnosis and possible histogenesis.

Case report

A 54 year old man presented with a three month history of lower abdominal pain and distension. There was no other medical history of note. Clinical examination and radiology revealed a palpable abdominal mass, which appeared to arise from the pelvis. At laparotomy a large retroperitoneal mass was excised. The tumour was noted to displace but not to infiltrate the bladder, right external iliac vessels, and right ureter.

Six weeks after surgery, the patient complained of lower backache. Imaging studies were considered highly suggestive of a lumbar metastasis. An isolated, probably metastatic, costal lesion was also identified. Local radiotherapy to the vertebra was followed by six courses of chemotherapy with adriamycin and ifosfamide.

Ten months after primary surgery, he re-presented with severe instability pain of the lumbar spine secondary to his metastatic disease. Palliative vertebral excision was undertaken and subsequent orthopaedic re-exploration revealed a recurrent pelvic tumour, together with peritoneal and hepatic metastases. The patient died 12 months after initial presentation. A necropsy was not performed.

Macroscopic appearances

The retroperitoneal tumour was a bosselated, firm, pale grey mass, which measured 140 × 95 × 80 mm and weighed 504 g. It had a variegated grey-white/yellow cut surface, with areas of yellow necrosis, and was partly covered by peritoneum. Representative tissue blocks were fixed in 10% neutral buffered formalin,

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Figure 1 Variable morphological appearances within the tumour. (A) Typical sclerosing epithelioid fibrosarcoma area. (B) Bland spindle cell (perineurial) area. (C) High grade epithelioid area. (Haematoxylin and eosin stained.)

Figure 2 Abrupt transition from epithelioid to spindle cell morphology. (Haematoxylin and eosin stained.)

routinely processed, and embedded in paraffin wax. Tissue sections were stained with haematoxylin and eosin.

Light microscopy

The tumour was non-encapsulated and largely well circumscribed, although infiltrating adjacent adipose tissue focally. It had a variable morphological appearance (fig 1). In some areas (~15%) it consisted of monomorphic cells arranged in cords, strands, and small nests, surrounded by conspicuous, focally hyalinised, collagenous stroma (fig 1A). In some of the tumour cell nests, loss of cellular cohesion resulted in a pseudoalveolar pattern. The tumour cells in these areas were rounded or oval and epithelioid in appearance, with a small to moderate amount of clear or pale eosinophilic cytoplasm. The tumour cell nuclei were often angulated but the chromatin was finely dispersed and nucleoli were inconspicuous. Mitotic activity in these areas was low (up to four mitoses/mm²). In several fields, these epithelioid areas were vaguely lobulated and surrounded by a spindle cell component (~15%), composed of bland, elongated, sometimes wavy cells, with little cytoplasm, in a collagenous background, arranged in a vague intersecting fascicular pattern (figs 1B, 2). There were no densely cellular spindle cell areas typical of conventional fibrosarcoma. In addition, there were large areas of tumour necrosis (~45%), and here the surrounding viable tumour (~25%) was densely cellular; there was nuclear hyperchromasia and brisk mitotic activity (up to 89 mitoses/mm²), although with retention of an epithelioid morphology (fig 1C). Vascular space invasion was

Figure 3 Electron micrograph of bland spindle cell area showing multiple aligned cell processes (arrows) typical of perineurial differentiation (original magnification, $\times 7500$) and (inset) detail of cell surface showing lamina (arrows) (original magnification, $\times 18\,000$).

not identified and local excision was just complete. Using the method of Trojani *et al*,⁶ the tumour was a grade 3 sarcoma.

Vertebral tissue, recurrent pelvic tumour, and peritoneal biopsies submitted at subsequent surgical explorations revealed metastases of high grade sarcoma with an epithelioid morphology, similar in appearance to the high grade cellular foci in the primary pelvic neoplasm.

Immunohistochemical findings

The tumour cells in all areas stained positively for vimentin and weakly positive for CD99. The epithelioid areas alone stained weakly positive for neurone specific enolase (NSE). The spindle cell areas alone stained weakly positive for epithelial membrane antigen (EMA). S100 protein, desmin, α -smooth muscle actin, CD34, and cytokeratin staining was negative in all areas.

Electron microscopy

Tissue was retrieved from formalin for electron microscopy, osmicated, stained en bloc overnight in 0.5% aqueous uranyl acetate, dehydrated in ethanol, and embedded in Agar 100 epoxy resin. Ultrathin sections were stained in aqueous uranyl acetate and Reynold's lead citrate. Tumour cells from the typical sclerosing epithelioid sarcoma areas contained prominent rough endoplasmic reticulum (RER) and lacked a clearly defined external lamina. Thus, they had an ultrastructure consistent with fibroblastic differentiation. In the bland spindle cell areas, tumour cells contained less RER but had many non-bundling intermediate filaments (of "vimentin" type) in the perinuclear cytoplasm. Parallel arrays of long slender processes were present (fig 3) and external lamina was seen focally over a proportion of cells (fig 3, inset), features suggestive of nerve sheath (specifically perineurial) differentiation. Myofilaments and epithelial features were absent from both areas.

Discussion

Based on morphological, immunohistochemical, and ultrastructural features, the bland epithelioid part of the tumour we have described conforms to the descriptions and illustrations previously published of sclerosing epithelioid fibrosarcoma.¹⁻³ This case is unusual, however, in three respects. It has areas of high grade morphology with large zones of tumour necrosis, surrounded by highly cellular and mitotically active epithelioid areas. In addition, the intermixed but separate bland spindle cell areas lack the cellularity, cytological features, and paucity of stroma typical of classic fibrosarcoma, and both immunohistochemically (EMA positivity) and ultrastructurally (aligned slender processes and lamina) display features of nerve sheath (specifically perineurial) differentiation.

The presence of small foci of necrosis has been described in some of the previously published reports of sclerosing epithelioid fibrosarcoma.^{1-3,5} In our case, not only were these

areas more extensive, but they were surrounded by more obviously malignant epithelioid areas, indicative of a higher grade tumour, a feature not described previously. Indeed previous publications¹⁻³ have stressed relatively bland cytological features and the risk of erroneous benign diagnoses.

Previous reports have suggested that sclerosing epithelioid fibrosarcomas are relatively indolent malignant neoplasms.¹⁻³ The establishment of metastasis in our case soon after primary tumour excision and short survival indicate that this may not always be the case.

The variability in immunophenotype of sclerosing epithelioid fibrosarcoma has been highlighted previously. Although vimentin positivity is usual, variable but often weak and/or focal positivity has also been documented for EMA,^{1,2} S100 protein,^{1,2,5} NSE,¹ and cytokeratins.^{1,2} This raises questions about the fibroblastic nature of the tumour, the criteria for diagnosis, and whether sclerosing epithelioid fibrosarcoma is an entity or merely a phenomenon associated with more than one line of differentiation. Eyden and colleagues³ suggested that tumours with typical sclerosing epithelioid fibrosarcoma morphology, which were positive for vimentin only, could safely be regarded as true (or "pure") sclerosing epithelioid fibrosarcomas. In cases where there was an anomalous immunophenotype, ultrastructural confirmation of the fibroblastic nature of the tumour cells was needed to permit a confident diagnosis of sclerosing epithelioid fibrosarcoma.

The possibility of nerve sheath differentiation in some cases, based on immunophenotype, has been raised previously,^{1,2} but in both publications this was dismissed on ultrastructural grounds. Our case is the first to be described in which immunohistochemical and ultrastructural features, in conjunction with morphological appearances in some parts of the tumour, support such a possibility. The parallel arrangement of cytoplasmic processes, although only focally well developed in our case, is a perineurial characteristic, contrasting

with the interdigitating and branching processes of typical Schwann cells,^{7,8} and supported the EMA positive, S-100 protein negative immunophenotype, which is typical of perineurial differentiation.

The presence of perineurial features in this case lends support to the previous proposal that "pure" and, by implication, "impure" (phenotypically heterogeneous) forms of sclerosing epithelioid fibrosarcoma may exist.³ We suggest that the distinctive morphological appearances of these tumours may be shared by neoplasms of various cell lineages, in our case showing nerve sheath (perineurial) differentiation, and that this is analogous to expression of the rhabdoid phenotype by a diverse range of malignant neoplasms. This may in part explain the variable immunophenotypes reported,¹⁻⁵ and the occasional diversity of ultrastructural characteristics observed.¹

Thorough tumour sampling and detailed immunohistochemical, ultrastructural, and genetic studies of further cases are needed to define the apparently inherent phenotypic heterogeneity of these tumours, and to determine whether sclerosing epithelioid fibrosarcoma is an entity or morphological variant associated with both fibroblastic and non-fibroblastic lines of differentiation.

- 1 Meis-Kindblom JM, Kindblom L-G, Enzinger FM. Sclerosing epithelioid fibrosarcoma. A variant of fibrosarcoma simulating carcinoma. *Am J Surg Pathol* 1995;19:979-93.
- 2 Reid R, Barrett A, Hamblen DL. Sclerosing epithelioid fibrosarcoma. *Histopathology* 1996;28:451-5.
- 3 Eyden BP, Manson C, Banerjee SS, et al. Sclerosing epithelioid fibrosarcoma: a study of five cases emphasizing diagnostic criteria. *Histopathology* 1998;33:354-60.
- 4 Christensen DR, Ramsamooj R, Gilbert TJ. Sclerosing epithelioid fibrosarcoma: short T2 on MR imaging. *Skeletal Radiol* 1997;26:619-21.
- 5 Gisselsson D, Andreasson P, Meis-Kindblom JM, et al. Amplification of 12q13 and 12q15 sequences in a sclerosing epithelioid fibrosarcoma. *Cancer Genet Cytogenet* 1998;107:102-6.
- 6 Trojani M, Contesso G, Coindre JM, et al. Soft-tissue sarcomas of adults: study of pathological prognostic variables and definition of a histopathological grading system. *Int J Cancer* 1984;33:37-42.
- 7 Erlandson RA. Perineurioma. In: *Diagnostic transmission electron microscopy of tumors*. New York: Raven Press, 1994: 632-34.
- 8 Erlandson RA. Schwann cell neoplasms. In: *Diagnostic transmission electron microscopy of tumors*. New York: Raven Press, 1994:710-17.