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CORRESPONDENCE

Malignant extraneural soft tissue perineurioma with striking microvascular proliferation

Sir,

Perineurioma is an uncommon variant of peripheral nerve sheath tumour composed predominantly of perineurial cells. Malignant perineurioma is exceedingly rare. A case of malignant extraneural soft tissue perineurioma is described which arose on the lower left leg of an 83-year-old woman. There was striking microvascular proliferation, which seems to be a novel feature in this case.

The palpable mass of unclear duration, measured $53 \times 36 \times 7$ mm at ultrasound and was determined to be solid, hypoechoeic, heterogeneous, and to reside in the deep subcutaneous layer, superficial to fascia and adjacent to the tibialis anterior muscle. The surrounding adipose tissue was reported to appear oedematous and hyperaemic. Diagnostic and attempted excision biopsy was performed and the laboratory received three nodular pieces of grey/white rubbery mucoid tissue and adipose tissue measuring $25 \times 20 \times 8$ mm in aggregate dimension following fixation in 10% neutral buffered formalin.

Histologically (Fig. 1) there were multiple fragments of a nodular, variably cellular myxoid tumour, which was mostly well defined, but focally intermingled with adipose tissue. The tumour was composed of spindle cells with elongated nuclei and delicate long thin biphasic cytoplasmic processes arranged in a fascicular and somewhat wavy and whorling lamellar fashion in a predominantly myxoid background. There was variable nuclear atypia ranging from mild through to marked with highly pleomorphic and multinucleated tumour cells, many of the latter aggregating around prominent small proliferating vessels. Mitoses, including occasional atypical forms, numbered up to 11/10HPF. Component vessels were of various sizes, but there were no arcuate arrangements. No necrosis was seen. The component of the tumour that infiltrated adipose tissue showed marked pleomorphism. No accompanying nerve was seen.

Immunohistochemical markers performed (Fig. 2) demonstrated that the delicate elongated tumour cells expressed epithelial membrane antigen (EMA) and CD34, although the pleomorphic perivascular cells were non-reactive with these immunomarkers. The MIB-1/Ki-67 determined proliferation index (PI) was approximately 70%. Other immunomarkers performed were non-reactive (S100, SOX-10, HMB45, Melan-A, cytokeratins AE1/AE3 and CK8/18, actin, smooth muscle actin, desmin, CD31 and mucin-4). An external laboratory kindly performed human erythrocyte glucose transporter 1 (GLUT1) and tight junction associated protein (Claudin-1) immunohistochemical markers. They were diffusely and focally expressed, respectively.

In view of the histological appearance and immunoprofile, the tumour was believed to be of perineurial origin and because of the pleomorphism, mitotic activity and high proliferation index, was diagnosed as a malignant extraneural soft tissue perineurioma (of ordinary type), and of intermediate grade according to the FNCLCC grading system, and WHO grade II. Complete and wide re-excision was recommended.

The patient was referred to a specialist sarcoma surgeon. Re-excision was performed $3^1/_2$ weeks following the initial biopsy. The specimen comprised skin with underlying subcutis, fascia and skeletal muscle and measured $115 \times 30 \times 30$ mm deep. Residual ill-defined myxoid appearing tumour was noted up to 25 mm in size within the subcutis (Fig. 3A). Tissue was

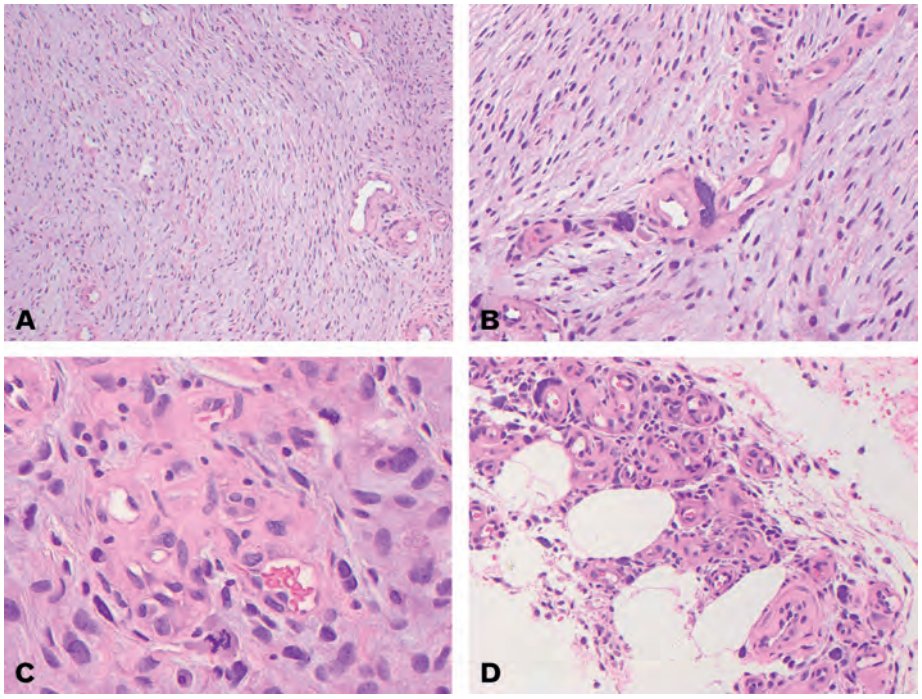

Fig. 1 Histological images of malignant perineurioma (H&E). (A) Elongated spindle cells in a pale myxoid background. (B) Pleomorphic cells in a perivascular arrangement associated with microvascular proliferation. (C) Pleomorphism and mitoses including atypical forms. (D) Permeation of adipose tissue.

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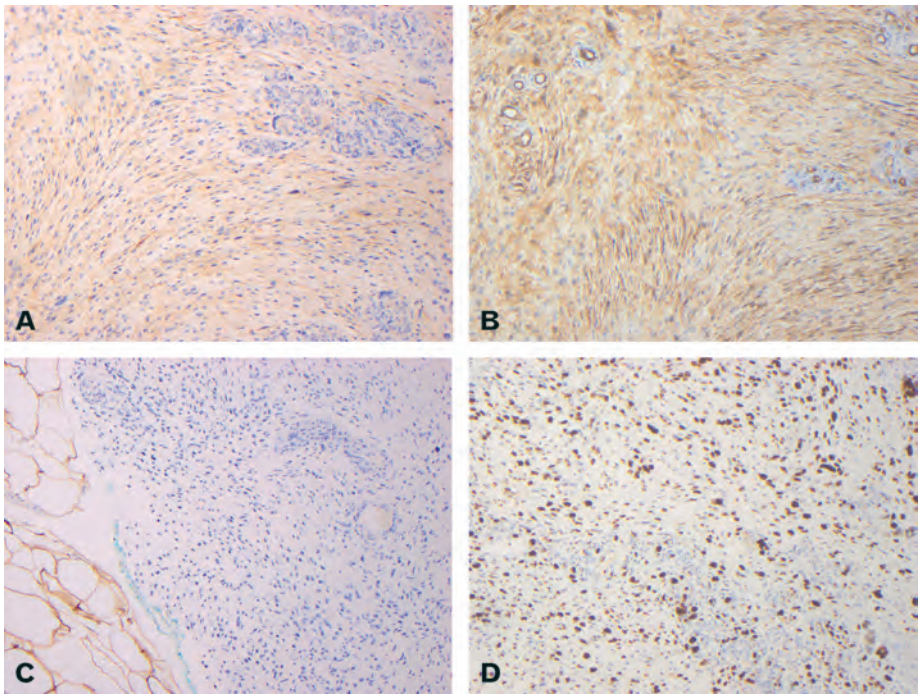

Fig. 2 Immunohistochemistry of malignant perineurioma. (A) EMA expression by spindle cells with poor expression by pleomorphic cells. (B) CD34 expression by spindle cells (positive internal control in endothelial cells). (C) S100 not expressed (positive internal control in adipose tissue). (D) MIB-1/Ki-67 proliferation index 70%.

taken for electron microscopy and the remaining specimen was fixed in 10% neutral buffered formalin. Histologically (Fig. 3B), the tumour had a similar morphological and immunohistochemical profile as seen in the initial biopsy, with a striking microvascular proliferation and adjacent pleomorphic cells. Tumour cells permeated fat within a myxoid background and in areas closely mimicked myxofibrosarcoma. It extended to several margins. Electron microscopy was reported as being compatible with a malignant peripheral nerve sheath tumour, of no specific type, perhaps reflecting tissue sampling or the degree of tumour differentiation. A diagnosis of malignant soft tissue perineurioma was maintained although it was acknowledged that myxofibrosarcoma could easily be entertained as an alternative diagnosis, were there not such strong EMA (and CD34) expression. Further re-excision was performed and no further lesion was identified.

The perineurium of peripheral nerve fascicles comprises perineurial cells with distinct ultrastructural features such as distinct, thin, non-branching cytoplasmic processes coated by an external lamina, and contain numerous pinocytic vescicles, actin and vimentin filaments, but few organelles. Their thin cytoplasmic processes are joined at their ends by tight junctions.[1] The formation of tight junctions is unique to perineurial cells and endothelial cells.[2] They are immunoreactive for vimentin and particularly epithelial membrane antigen (EMA), but also consistently express GLUT1 and Claudin-1.[1–7] The origin of the perineurial cell is debated, but origin from fibroblasts, Schwann cells or arachnoid cells have all been postulated.[1]

Reactive or neoplastic perineurial cells have been demonstrated ultrastructurally and immunohistochemistically in a number of pathological processes including reactive lesions (Morton's neuroma, Pacinian neuroma) and neoplastic lesions, as a component of neurofibroma, dermal nerve sheath myxoma/neurothekeoma and perineurioma.[1] The immunophenotype of perineurioma parallels that of the normal perineurial cell.[2]

Perineurioma is generally benign and divided into intraneural perineurioma (previously confused with localised hypertrophic neuropathy)[8] and soft tissue forms, which are unrelated to nerves (extraneural soft tissue perineurioma, ESTP), each of which generally behaves in a benign fashion. Intraneural perineurioma is composed of perineurial cells within the

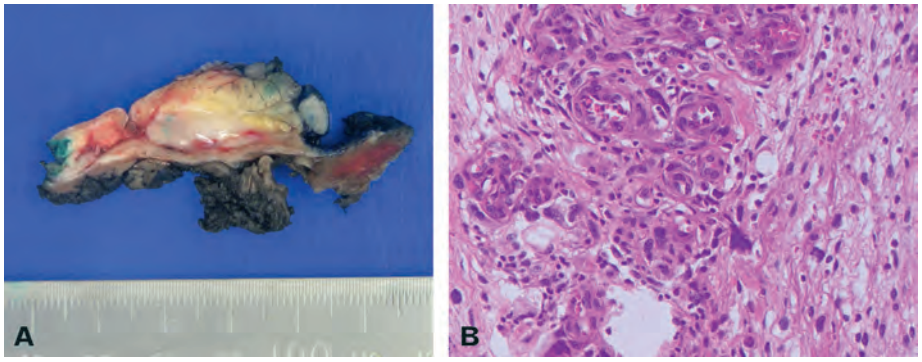

Fig. 3 Excision biopsy of remaining malignant perineurioma. (A) Macroscopic image of cut surface demonstrating a mucoid appearance. (B) The microscopic findings were similar to the diagnostic biopsy with variable pleomorphism, microvascular proliferation and mitotic activity (H&E).