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Case report

Nerve sheath myxoma of the breast

A light and electron microscopic, histochemical and immunohistochemical study

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Summary. A nerve sheath myxoma involving the breast has been examined by light and electron microscopy, and by immunohistochemical and histochemical methods. Electron microscopically, cells with features indicative of Schwann cells, perineural cells and fibroblasts were identified in the tumour and S-100 protein and vimentin positivity was demonstrated in the tumour cells. The mucoid matrix stained positive for chondroitin-4 or 6-sulphate in keeping with a cartilaginous lesion. These findings are discussed in relation to the uncertain histogenesis and the differential diagnoses of the tumour in the breast.

Key words: Breast tumour – Myxoma – Nerve sheath tumour – Neurothekeoma

Introduction

Nerve sheath myxoma is an uncommon lesion, most often arising on the face or upper extremities (Gallager and Helwig 1980; Pulitzer and Reed 1985). The unusual sites of occurrence for this benign tumour include trunk, lower extremities, vulva (Pulitzer and Reed 1985), oral cavity (Mason et al. 1986) and tongue (Mincer and Spears 1974). No case of nerve sheath myxoma involving the breast has been reported.

The purpose of this article is to report what we believe is the first case of this rare lesion involving the breast.

Case report

A 20-year-old Chinese woman presented with a right breast lump of 6-months duration. It had been growing slowly and was occasionally painful. There was no past medical or family history of any relevance.

Physical examination revealed a soft lobulated mass in the lower aspect of the right breast pushing the inferior part of the areola upwards. The areolar and adjoining skin over the lump was stretched but not ulcerated. There were no palpable regional lymph nodes and the patient had no stigmata of von Recklinghausen's neurofibromatosis (Riccardi 1981). The preoperative diagnosis was a lipoma and a local excision was performed.

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Materials and methods

The excised breast lump was received in 10% buffered formaldehyde and routinely processed. Sections were stained with haematoxylin and eosin, periodic acid-Schiff (PAS) with and without diastase digestion, Alcian blue at pH 2.5, reticulin (Gordon and Sweet's method), Masson trichrome, Palmgren's method, Luxol Fast Blue and Bodian's method.

Further sections were examined by an indirect immunoperoxidase (PAP) technique (Sternberger 1979) using polyclonal rabbit anti-human antiserum to S-100 protein, anti-cytokeratin (Dako Corp., dilution 1:100), monoclonal antibodies to vimentin (Dako Corp., dilution 1:200), CAM 5.2 (Becton Dickenson, dilution 1:50), chondroitin sulphate (Bio-yeda) and HNK-1 (WHO immunology centre). Negative control staining was obtained by using non-immunized serum with phosphate buffered saline and appropriate positive controls for these reagents were also used.

Finally tissue blocks recovered from formalin-fixed specimen were processed for electron microscopy and examined in a Phillips 400-TEM.

Results

The specimen consisted of a $6 \times 5 \times 4$ cm lesion with an ellipse of overlying areolar skin. The cut surface was greyish and showed a rather myxoid nodular lesion with an extension to the deep resection margin. The nodules of tumour tissue ranged from 1 to 2 mm in diameter and the appearance of these nodules was highly reminiscent of 'fish roe' or 'sago' (Fig. 1).

Microscopically, the lesion had a multilobu-

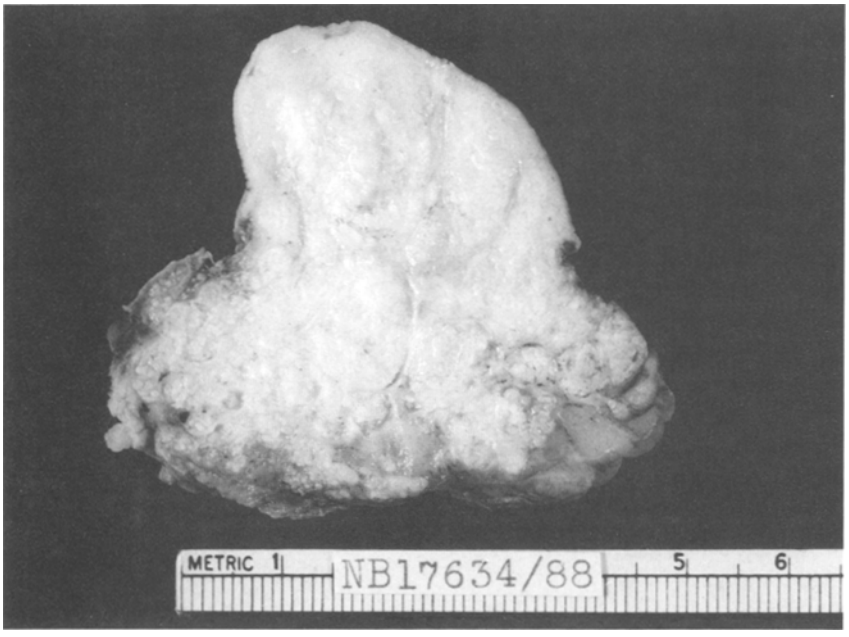

Fig. 1. Lobulated myxoid nodular tumour of the breast

lated appearance. The tumour nodules, which were of varying sizes, were separated by variable fibrous septae containing delicate small blood vessels (Fig. 2a). Each lobule was composed of spindle and stellate cells lying within an abundant slightly basophilic myxoid matrix. The cells had small, rather elongated nuclei with occasional nucleoli and the cytoplasm was pale with indistinct cell borders. An occasional normal mitosis was seen in the tumour cells (Fig. 2b). Scattered within and around the tumour nodules were occasional lymphocytes, plasma cells and mast cells.

The tumour nodules were in close contact with areolar skin appendages and breast ductules but these were never invaded by the tumour. There was no direct continuity between the tumour nodules and nerves nor were there focal changes in the nerves similar to the tumour itself. Although most of the tumour tissue was located within the breast parenchyma, an origin from areolar skin and subcutis with extension into the breast cannot be excluded.

Histochemically the sections revealed tiny amounts of PAS-positive diastase-labile intracytoplasmic glycogen in tumour cells. Nerve fibres and nerve endings (Bodian's method), axon fibres (Palmgren's method) and myelin sheath (Luxol Fast Blue) were not identified in the tumour nodules. The myxoid matrix was Alcian blue positive.

Immunocytochemically the tumour cells stained positive for S-100 protein and vimentin (Fig. 3a, b). CAM 5.2, anti-cytokeratin, anti-neurofilament protein, alpha$_1$-antitrypsin, alpha$_1$-antichymotrypsin and HNK-1 antibodies were negative. The monoclonal anti-chondroitin-sulphate which specifically stains chondroitin-4 or 6-sulphate but not dermatan sulphate showed positivity in the myxoid matrix, suggesting cartilaginous origin or differentiation.

The tumour cells were generally spindle-shaped and widely dissociated from each other on electronmicroscopic examination. Some cells had cytoplasmic extensions of varying complexity with infolding of the cell membrane and sometimes enfolding stromal collagen bundles with "mesocollagen" formation, reminiscent of mesoaxon structures (Fig. 4a). Cell junctions and investing external basal lamina were not identified. Rough endoplasmic reticulum was inconspicuous. Other cells identified in the tumour had long thin bipolar cell processes lacking infoldings, cell junctions and basal lamina (Fig. 4b). Some of these bipolar cells showed evidence of collagen production (Fig. 4c). These ultrastructural features are reminiscent of Schwann cells, perineural cells and fibroblasts.

Discussion

Nerve sheath myxoma was first described as a specific pathological entity by Harkin and Reed in 1969. Subsequently, lesions of similar histological features were described as Pacinian neurofibroma (MacDonald and Wilson-Jones 1977), bizarre cutaneous neurofibroma (King and Barr 1980), neurothekeoma (Gallager and Helwig 1980), cutaneous lobular neuromyxoma (Holden et al. 1982) and myxoid tumour of the nerve sheath (Enzinger and Weiss 1983). These alternative terms are prob-

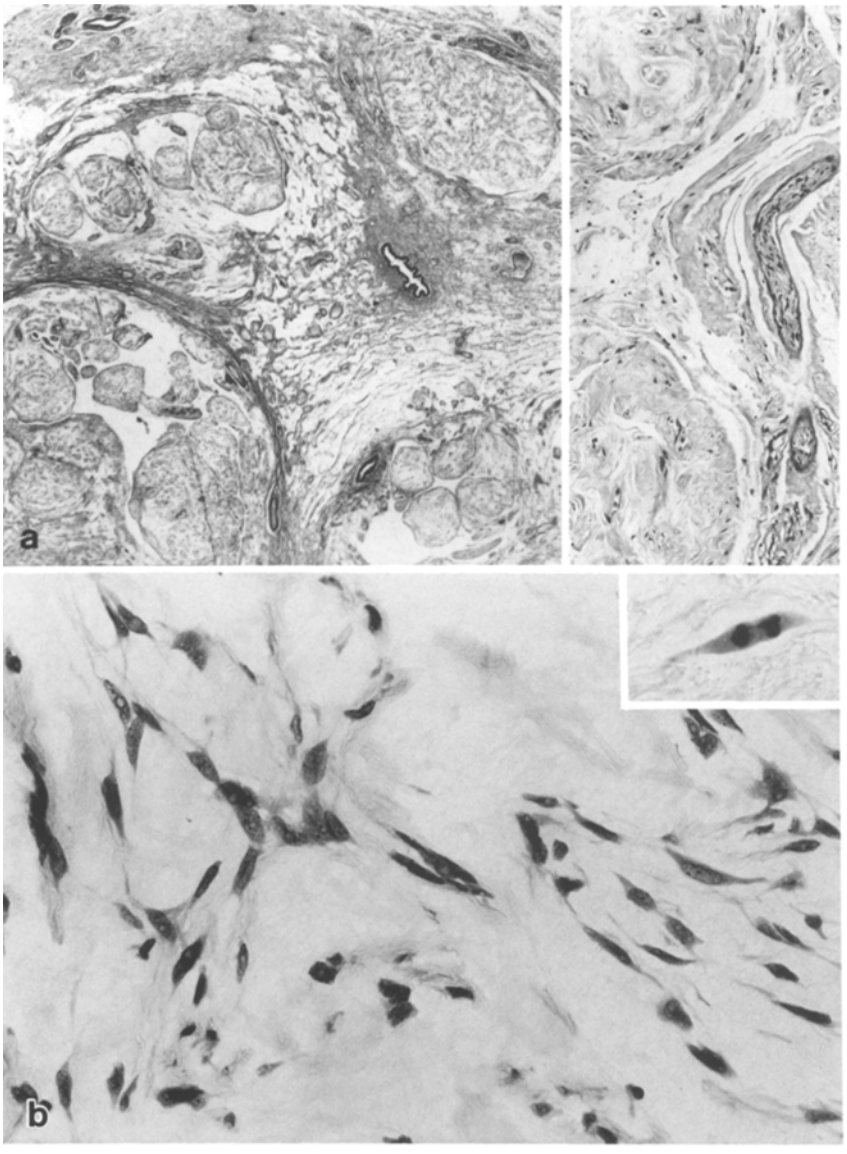

Fig. 2. a Lobules of myxoid tumour of varying sizes amidst breast ductules (*Left. H & E ×10*) and adjacent nerves appear normal (*Right. H & E ×60*). **b** Spindle and stellate cells with mild cytologic atypia lying within an abundant myxoid matrix. (H & E ×400). An occasional normal mitosis is present (*Inset. H & E ×600*)

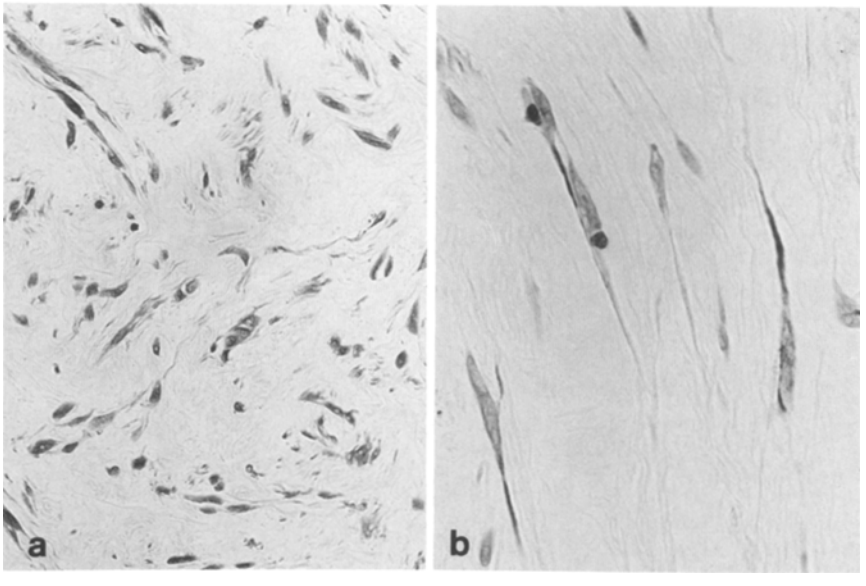

Fig. 3. a Positive immunostaining for S-100 protein (×300) and **b** vimentin (×600) in some of the tumour cells

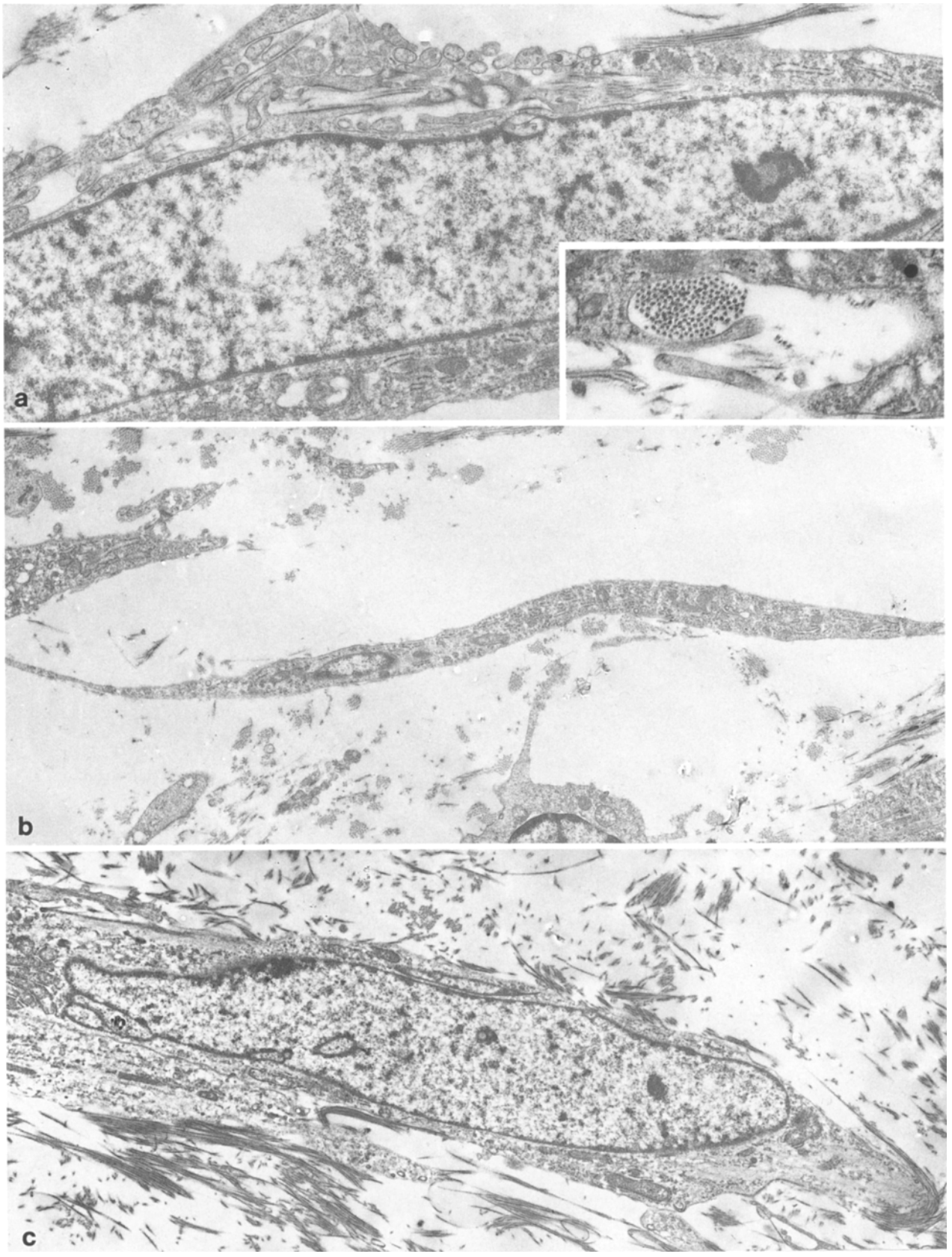

Fig. 4. **a** An elongated neoplastic cell showing complex cytoplasmic extensions with infolding of the cell membrane. (×12880) and occasionally enfolding stromal collagen bundles with "mesocollagen" formation. (*Inset.* ×*22480*). **b** An elongated cell with long thin bipolar cell processes. (×7670). **c** An elongated cell showing collagen production. (×6580)

ably an attempt to incorporate concepts of pathogenesis in terminology.

The precise nature of nerve sheath myxoma remains uncertain. The demonstration of focal changes in adjacent nerves which are histologically similar to the tumour itself (Harkin and Reed 1969; Gallager and Helwig 1980; Fletcher et al. 1986) strongly suggests a nerve sheath origin for these tumours. However, the ultrastructural and immunohistochemical features noted in our case suggest that nerve sheath myxoma may be derived either from Schwann cells (Gallager and Helwig 1980) or from perineural fibroblasts (Webb 1979). The demonstration of chondroitin-4 or 6-sulphate in the mucoid matrix of the tumour indicative of cartilaginous origin or differentiation (Angervall et al. 1984; Fletcher et al. 1986) further complicates the histogenesis of this tumour. It seems unlikely that nerve sheath myxoma is derived from three different types of cells, but seems much more probable that a primitive mesenchymal cell, with totipotential capacity, may be the origin.

Nerve sheath myxomas are benign lesions, although local recurrences may complicate incomplete excision (Gallager and Helwig 1980; Pulitzer and Reed 1985). The macroscopic and light microscopic appearances of the tumour described in our case are typical and agree well with previous descriptions. The differential diagnoses which should be considered in this respect include fibroadenoma with marked myxoid change, myxoid neurofibroma or plexiform neurofibromatosis, myxoma of the breast, myxoid liposarcoma and myxoid variant of malignant fibrous histiocytoma.

Fibroadenoma is a common benign lesion of the breast at this age and extensive myxoid change may occur occasionally in this tumour. However, epithelial components are nearly always present. Myxoma of the breast (Chan et al. 1986) hardly ever forms nodules, whereas myxoma of the nerve sheath often forms multiple myxoid nodules separated from each other by fibrous septa. Myxoid neurofibroma lacks a lobular pattern, has an obvious fibrillary background and usually contains nerve fibres within the tumour.

Myxoid liposarcoma may rarely occur in the breast (Kristensen and Kryger 1978) and can be differentiated from nerve sheath myxoma by its vascular plexiform capillary pattern and the presence of lipoblasts. The diagnosis of myxoid variant of malignant fibrous histiocytoma depends on the presence of diagnostic features like large pleomorphic malignant histiocytic cells and a characteristic storiform pattern somewhere in the tumour. None of these features are present in this case.

In conclusion, we believe that the myxoid tumour in our case is a true nerve sheath myxoma involving the breast. The histogenesis of this tumour is not clear but our findings suggest that it is a tumour of primitive mesenchyme. Nerve sheath myxoma can be readily recognized as a distinct entity by light microscopy, even though immunohistochemical features and ultrastructural morphology may differ due to inherent totipotential capacity of differentiation of the primitive mesenchymal cell.

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