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CASE REPORT

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An unusual case of benign thyroid tumour consisting of epithelial and nonepithelial components

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Abstract An encapsulated tumour consisting of follicular epithelial cells, fat-laden round cells and spindle cells was found in the right lobe of the thyroid gland of a 66-year-old woman. The follicular epithelial cells had oxyphilic cytoplasm in which numerous mitochondria were densely packed. The fat-laden round cells were indistinguishable from mature fat cells by light microscopy. However, they were immunohistochemically negative for S-100 protein and epithelial markers, and lacked a continuous basement membrane. The spindle cells embedded in the collagenous matrix possessed well-developed rough endoplasmic reticulum, most of which contained variably sized, non-membrane-bound lipid droplets. Bundles of thin filaments were occasionally observed in the cytoplasm. Some spindle cells were immunoreactive for PCNA and α-smooth muscle actin. There was no striking nuclear atypia of the tumour cells and no capsular or vascular invasion by these components. The tumour can be classified as a benign mixed tumour.

Key words Thyroid · Mixed tumour, benign · Fat

Introduction

Benign tumours composed of both epithelial and mesenchymal components are rare in the thyroid gland. Such tumours include adenolipoma [7, 10, 11, 13, 18] and adenochondroma [22, 23]. We recently experienced a very unusual case of a benign thyroid tumour consisting of follicular epithelial cells, fat-laden round cells and spindle cells. To our knowledge, there are no similar reports in the literature.

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Clinical history

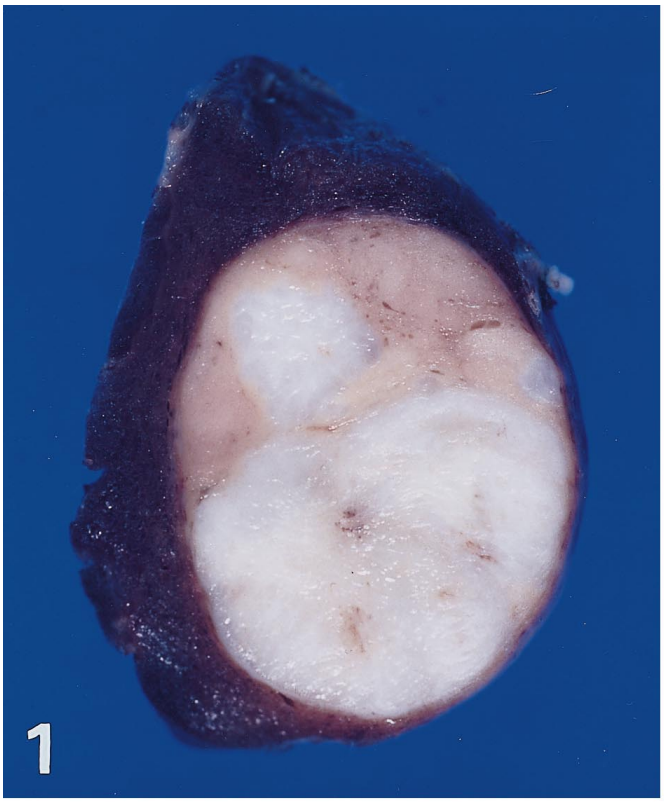
A 66-year-old woman attended Neagari General Hospital for examination of a swelling in her anterior neck, which had first been noted 1 month earlier. Computed tomography detected a sharply defined tumour in the right lobe of the thyroid gland. After the diagnosis of a 'spindle cell tumour' had been made by needle biopsy, the right lobe was removed surgically.

Materials and methods

For histological examination, formalin-fixed, paraffin-embedded tissue sections were stained with haematoxylin and eosin and with oil-red O. For immunohistochemical examination, tissue sections were stained with antibodies against α1-antirypsin (DAKO, Denmark), α-smooth muscle actin (DAKO, Denmark), bcl-2-associated X protein (Medical and Biological Laboratories, Japan), calcitonin (Immunonuclear, Minn., USA), chromogranin A (Boehringer Mannheim, Germany), cytokeratin CAM5.2 (Becton Dickinson, Calif., USA), chorioembryonic antigen (Nichirei, Japan), desmin (DAKO, Denmark), endothelial cell marker CD34 (Novocastra Laboratories, UK), epithelial membrane antigen (DAKO, Denmark), factor VIII (DAKO, Denmark), GFAP (DAKO, Denmark), HAM56 (gift from Dr. Gown, Washington University), HHF35 (gift from Dr. Gown), keratin DAKO, Calif.), laminin (Immunotech, France), myoglobin (DAKO, Calif.), neuron-specific enolase (IBL, Japan), proliferating cell nuclear antigen (PCNA) (DAKO, Denmark), p53 (Nichirei), S-100 (Nichrei), thyroglobulin (DAKO, Denmark), and vimentin (DAKO, Denmark). The formalin-fixed tumour tissue was osmicated and processed routinely for electron-microscopic study. Fluorescence in situ hybridization (FISH) was performed on the formalin-fixed, paraffin-embedded tissue sections according to the methods published by Ooi et al. [12]. Probes used were specific for the centromeric regions of chromosome 7 (D7Z1; Oncor, Md.) and chromosome 12 (D12Z3; Oncor).

Pathological findings

The cut surface of the right lobe of the thyroid gland showed an encapsulated, well demarcated tumour measuring 2.9×2.3×3.0 cm (Fig. 1). The tumour consisted of a light yellow and light grey, relatively firm, portion. The latter occupied approximately two-thirds of the mass.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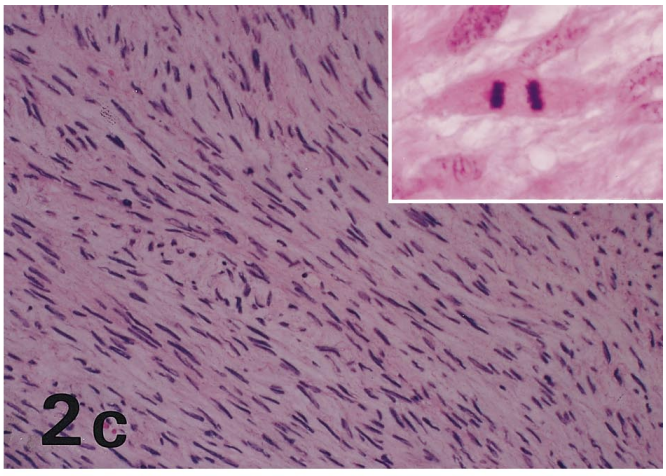
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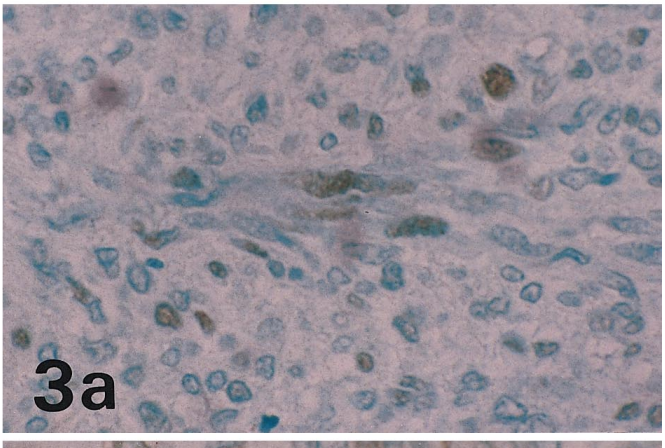
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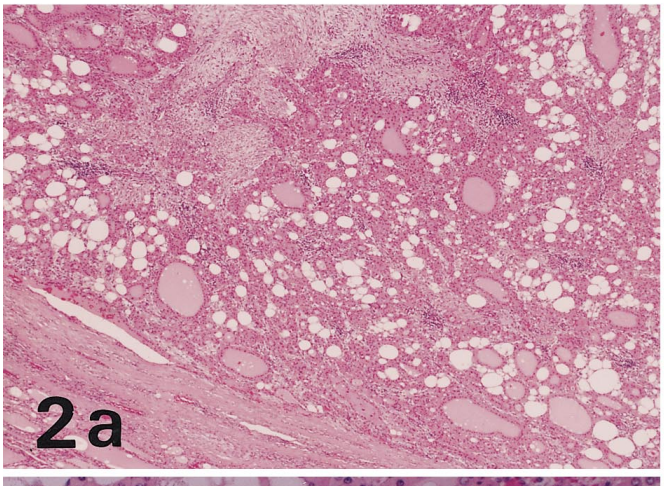
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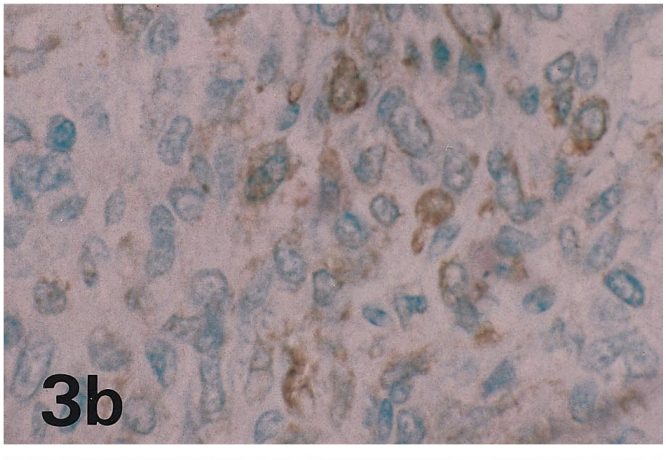
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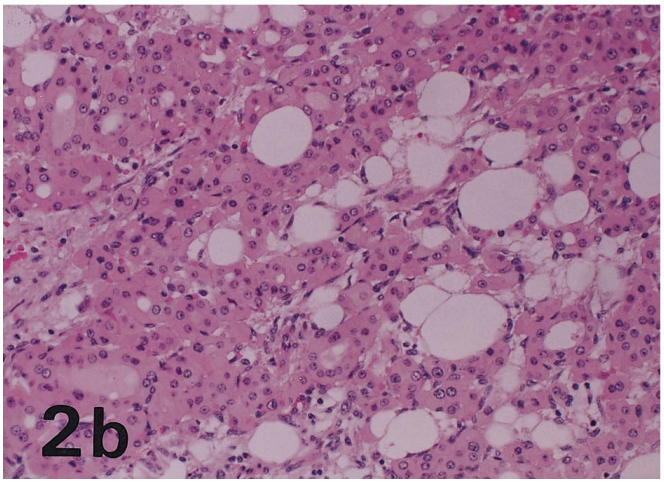
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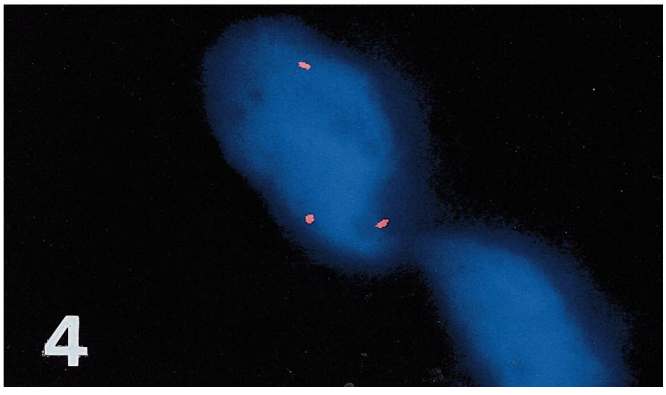
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On light microscopy the tumour was seen to be well circumscribed and separated from the compressed surrounding thyroid by a fibrous capsule (Fig 2). Epithelial cells and fat-laden round cells predominated in the light yellow portion. The epithelial cells, with oxyphilic cytoplasm, formed various sized follicles, small cell nests and trabeculae (Fig. 2b). Nuclear pleomorphism was not evident. There was no degeneration of the follicular cells. The fat-laden round cells, which light microscopy did not distinguish from mature fat cells , were intermingled with the follicular cells (Fig. 2b). Spindle cells, described below, were scattered . In the light grey, firm, portion, spindle cells predominated and proliferated, forming cellular bundles (Fig. 2c). Some spindle cells have eosinophilic cytoplasm. Mitoses were occasionally observed in the bundles of the spindle cells (approximately 5/cm^2 of field) (Fig. 2c), but there was no striking cellular pleomorphism. Mucoid materials and dense bundles of collagen were deposited focally in the extracellular space. Vascular proliferation was inconspicuous. Small numbers of the fat-laden round cells and the epithelial cells were also mixed in this portion. Oil red-O staining showed that a large number of the spindle cells contained positively-stained droplets, as did the fat-laden round cells.

Within the fibrous capsule of this tumour another tumour approximately 2 mm in diameter was found incidentally. The second tumour was composed of columnar or cuboidal cells with nuclei with a ground glass appearance, nuclear grooves and intranuclear cytoplasmic inclusions. The cells showed papillary and follicular growth patterns. This lesion was diagnosed as an occult papillary carcinoma (figures not shown).

Amyloid deposition was not observed in the tumour or in the surrounding thyroid tissue. No adipose tissue was present in the surrounding thyroid tissue.

There was no clinical evidence of metastasis.

Immunohistochemically the follicular cells were positive for thyroglobulin. The spindle cells were positive for vimentin, and some were positive for PCNA (Fig. 3a), α-smooth muscle actin (Fig. 3b) and HHF35, but negative for the endothelial cell marker CD34. The fat-laden round cells were discontinuously outlined with anti-laminin antibody. Most of the spindle cells were not accompanied by laminin. None of the tumour cells was stained with anti-S100 protein antibody. No reactivity for epithelial markers, such as epithelial membrane antigen, keratin and thyroglobulin was detected in the fat-laden round cells or the spindle cells.

In fluorescence in situ hybridization (FISH), the follicular cells of the tumour showed disomies of chromosomes 7 and 12. Most of the spindle tumour cells were disomic, but there were a few with trisomies of chromosome 7 (Fig. 4). Polysomy of chromosome 12 was not detected in spindle cells. Identification of the nuclei of fat-laden cells was so difficult in tissue sections treated for FISH that the chromosome alterations cannot be estimated.

Electron microscopy showed that the epithelial cells had many mitochondria in the cytoplasm (Fig. 5a). Secretory granules had accumulated near the apical portion of the epithelial cells forming the wall of the follicles and the slender microvilli projected into the lumen. Lipid droplets were rarely seen in the epithelial cells. The epithelial cells, joined together by intercellular junctions, were surrounded by continuous basement membrane. The spindle cells possessed well-developed rough endoplasmic reticulum, most of which contained various sized, non-membrane-bound lipid droplets and some of which also had bundels of thin filaments (Fig. 5b). Some lipid droplets had fused together to become larger ones. Neither intercellular junctional complex nor microvilli were identified. The spindle cells were embedded in collagenous extracellular matrix, and patchy basement membrane was detected on the cell surface of some spindle cells. Medium-sized or large round cells containing large lipid droplets were intermingled with the epithelial and spindle cells (Fig. 5c). The other cytoplasmic organelles and the nucleus were displaced to the periphery in the fat-containing round cells. They showed a discontinuous basement membrane (Fig. 5d).

◀ **Fig. 1** Gross section the surgical specimen showing the encapsulated, well-demarcated tumour, which consisted of a light yellow and a light grey portion

Fig. 2 **a** Low-power magnification of the tumour, which was well circumscribed and separated from the surrounding thyroid tissue by a fibrous capsule. Surrounding tissue was compressed by the tumour. Haematoxylin-eosin, ×30 **b** The light yellow portion, which consisted mainly of epithelial cells and fat-laden round cells. Haematoxylin-eosin, ×150 **c** The light grey portion: predominantly spindle cells forming cellular bundles. Haematoxylin-eosin, ×150 *Inset* shows a mitosis. Haematoxylin-eosin, ×750

Fig. 3 **a** Immunohistochemical staining for PCNA. Some spindle cells were positive. ×600 **b** Immunohistochemical staining for α-smooth muscle actin. Some spindle cells were positive. ×600

Fig. 4 FISH with chromosome 7 centrometric probe on the spindle cells (rhodamine detection, *red signals*). Nucleus with trisomy for chromosome 7 was seen

Discussion

We described a very unusual case of thyroid tumour composed of follicular epithelial cells, fat-laden round cells and spindle cells. Although the presence of mitosis and immunopositivity for PCNA in the zone of spindle cells indicated that the spindle cells were more highly proliferative than the other two types of cells, there was no evidence suggesting malignancy. The tumour was well circumscribed, with a continuous fibrous capsule, and showed expansive growth, so that it can be interpreted as benign.

The follicular epithelial cells had oxyphilic cytoplasm in which numerous mitochondria were densely packed. They showed no remarkable cellular atypia. These features were similar to those of the oxyphilic cell type of thyroid adenoma [15]. They were morphologically different from the follicular cells in the surrounding, non-neoplastic thyroid tissue and were one of the distinctive components of this tumour. Criado et al. detected poly-

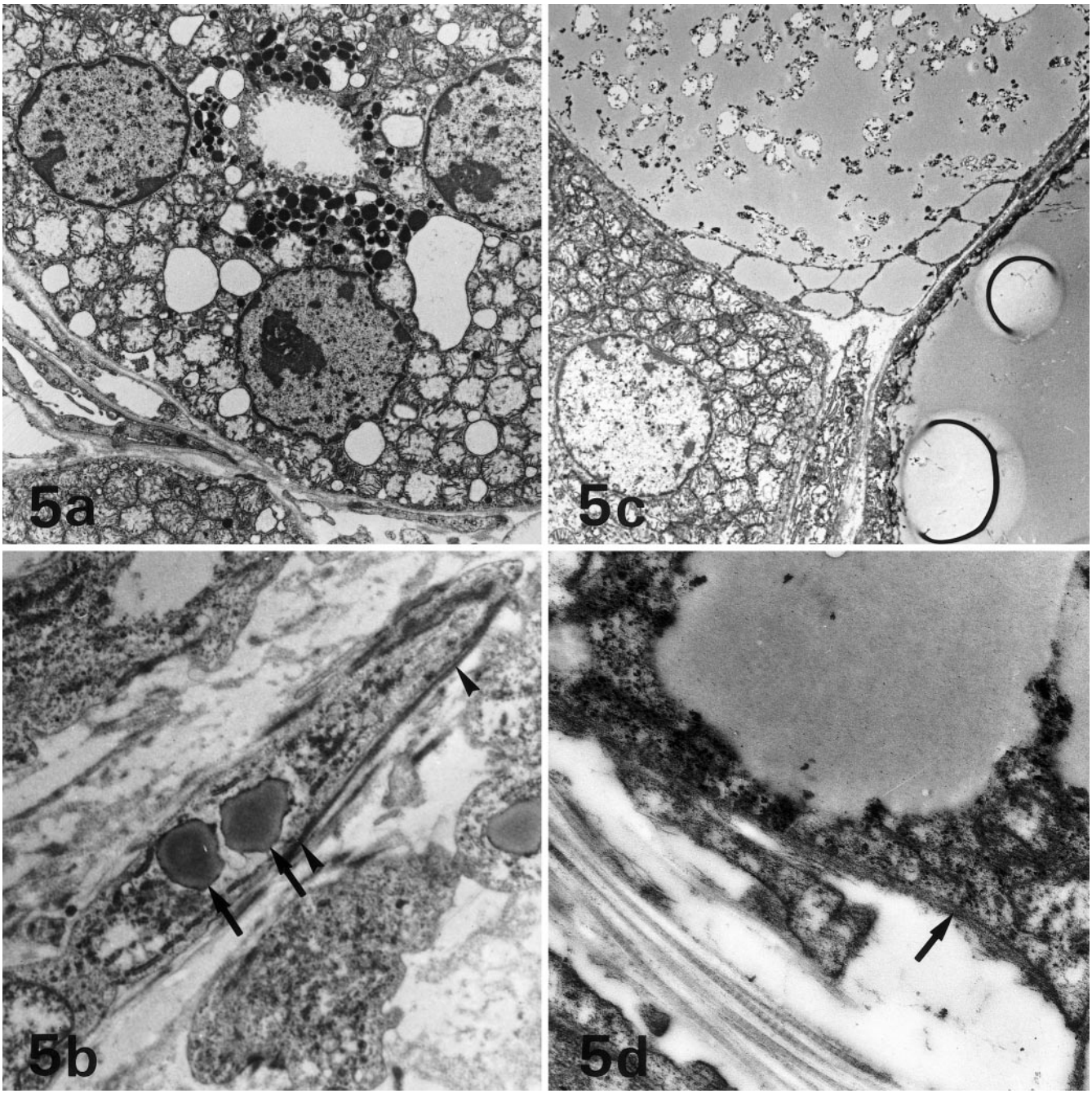

Fig. 5 **a** Ultrastructure of epithelial tumour cells. These cells had many mitochondria in the cytoplasm. ×3800 **b** Ultrastructure of spindle cells with non-membrane-bound lipid droplets (*arrows*) and bundles of thin filaments (*arrowheads*). ×7050 **c** Ultrastrucutre of round cells containing large lipid droplets. They were intermingled with epithelial tumour cells. ×4400 **d** A fat-containing round cell with a discontinuous basement membrane (*arrow*). ×22000

somy of chromosome 7 in 35.7% of thyroid follicular adenomas and chromosome 12 in 29.6% [1]. In the present case, however, follicular epithelial cells showing such polysomy were not found.

Under the light microscope, the fat-laden round cells were indistinguishable from mature fat cells. However, immunohistochemistry and electron microscopy revealed that they were negative for S-100 protein and lacked a continuous basement membrane, indicating that they were not mature fat cells. However, they had no immunoreactivity for epithelial markers, and regressive changes such as degeneration of the follicular cells and fibrosis were not observed within the area with mixed epithelial cells and fat-laden round cells. They were not ‘lipid-rich’ follicular epithelial cells formed by metaplastic transformation, as mentioned by Schröder et al. [19], but were of mesenchymal origin and made up the tumour. Lipid droplets, which occasionally developed into larger ones by coalescence, were detected in most of the spindle cells. The spindle cells, some of which showed numeri-

cal alteration of chromosome 7, were intermingled with the fat-laden round cells. These findings suggest that the fat-laden round cells and the spindle cells were on the same neoplastic, mesenchymal cell spectrum.

The nonepithelial components of the present tumour are light microscopically similar to solitary fibrous tumour (SFT) with lipomatous lesion of thyroid gland [20] or to the haemangiopericytoma-like lesions with significant adipocytic component [3]. However, immunohistochemistry and electron microscopy do allow differentiation of the nonepithelial components of the present tumour from the latter two lesions: the spindle cells of SFT are stained strongly and consistently positive for CD34 [4, 21], and tumour cells of adult haemangiopericytomas are devoid of myoid features [3]. In the present tumour, however, nonepithelial tumour cells were immunohistochemically negative for CD34, and some spindle cells had bundles of thin filaments and showed immunoreactivity for actin.

The spindle cells shared fibroblastic, fibrolipoblastic and myofibroblastic features. It is not unusual for fibroblasts to retain lipid droplets in some conditions, such as wound healing [14]. Fibroblasts also have the capacity to convert into myofibroblasts [5], and the spindle cells in the present tumour may thus have originated from stromal fibroblasts. However, it is believed that multipotential mesenchymal stem cells exist in the soft tissue stroma, particularly around the blood vessels. Such mesenchymal stem cells are thought to be involved in the histogenesis of some soft tissue tumours. Rossouw et al. [16] examined 15 cases of liposarcoma by electron microscopy and suggested that pleomorphic liposarcoma was derived from a mesenchymal stem cell. Iwasaki et al. [8] applied monoclonal antibodies generated to whole-cell antigens of a human malignant histiocytoma cell line and demonstrated that malignant histiocytoma shared antigenicity with perivascular mesenchymal cells and fibroblasts as well as liposarcoma. Thus, although the existence of mesenchymal stem cells in the thyroid remains unconfirmed, it is also possible to speculate that the spindle cells in the present case originated from the multipotential mesenchymal stem cells.

Thyroid lesions containing fat are not common. Rarely, ‘mature adipose tissue’ has been described within normal thyroid glands [9], adenomas [7, 10, 11, 13, 18], amyloid goitres [17] and thyroid carcinoma [2, 6]. However, without detailed analyses of the morphological features of fat-containing cells, the previous authors identified light microscopically the round cells with large fat vacuoles as mature adipose tissue. As shown in the present study, such round cells indistinguishable from mature fat cells by light microscopy may not always be sufficient immunohistochemical and ultrastructural features to interpret them as mature fat cells. It is necessary to scrutinize thyroid lesions with fat by immunohistochemistry and electron microscopy for a better understanding of the histogenesis.

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