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CASE REPORT

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Coexistence of papillary and medullary carcinoma of the thyroid gland-mixed or collision tumour? Clinicopathological analysis of three cases

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Abstract We present three thyroid carcinomas displaying medullary and papillary components. In two cases the papillary component was characterized by typical papillae with a fibrovascular core; in one a follicular variant of papillary carcinoma was found. The papillary component was dominant in two and the medullary in one case. One tumour showed clear-cut borders between the two components, the others displayed an intermingled pattern. Both tumour components were seen in lymph node metastases with immunostaining with antibodies to calcitonin, chromogranin A, carcinoembryonic antigen, other neuroendocrine markers and thyroglobulin. At least two of our cases are true mixed carcinomas probably arising from a common stem cell.

Key words Thyroid · Mixed medullary-papillary carcinoma · Common stem cell

Introduction

Carcinomas of the thyroid with different morphologic phenotypes are very rare. Most of them have been regarded as mixed medullary-follicular carcinomas (Hales et al. 1982; Ljungberg et al. 1983; Pfaltz et al. 1983) and, consequently, as variants of medullary carcinomas in the WHO classification of 1988. Albores-Saavedra et al. (1990) were the first to publish two cases of mixed medullary-papillary carcinoma with the papillary component presenting in a follicular pattern. We now report three cases of mixed medullary-papillary carcinoma, in two of which the papillary component consisted of typical branching papillae with a fibrovascular core covered by tumour cells.

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Case reports

In a 49-year-old woman the left lobe of the thyroid was removed because of a cold nodule which was first diagnosed 27 months before. Thallium uptake by the nodule was found and cytology revealed cell-rich material containing cells with nuclear pseudoinclusions. Calcitonin was undetectable in the serum and thyroglobulin (5.0 ng/ml) was normal, whereas carcinoembryonic antigen (CEA; 4.67 ng/ml) was slightly elevated. The frozen section diagnosis was follicular neoplasia and final diagnosis led to total thyroidectomy and radioiodine therapy. Three years after the operation the patient is alive with pulmonary metastases without iodine uptake.

In the second case a 49-year-old woman presented with a large multinodular goitre containing large scintigraphically cold areas. Total thyroidectomy was performed. Preoperatively multiple enlarged lymph nodes were palpable and were revealed on the CT scan. Serum levels of CEA (>60 ng/ml) and thyroglobulin (92.7 ng/ml) were markedly elevated, whereas calcitonin was undetectable. However, marked elevation of serum calcitonin (5–10 ng/ml) was seen postoperatively. Three years after the operation the patient died with multiple metastases.

The third case was a 28-year-old man from whose neck an enlarged lymph node was removed. Histological examination revealed metastatic papillary thyroid carcinoma. Subsequently a cold nodule was found in the upper half of the right lobe of the thyroid. Serum levels of calcitonin and CEA were not measured preoperatively. Total thyroidectomy, ipsilateral neck dissection and radioiodine therapy followed. Further lymph node metastases were removed 8 months later from the mediastinum, followed by radioiodine therapy. Nineteen months after the first operation, the patient is free of recurrent disease and alive.

Material and methods

After fixation in 10% buffered formaldehyde solution (pH 7.4) many samples representative of the whole tumour were processed conventionally and embedded in paraffin. Consecutive sections, 4 µm thick, were stained with haematoxylin and eosin and Congo red. In addition, immunohistochemistry was performed according to the avidin-biotin-peroxidase method using commercially available antibodies as indicated in Table 1.

Table 1 Range of antibodies used for immunohistochemistry (*ACTH* Adrenocorticotropic hormone; *CEA* carcinoembryonic antigen; *GRP* gastrin releasing peptide; *NSE* neuron-specific enolase)

Antibody to	Source	Dilution
Thyroglobulin	Dakopatts	1: 100
Calcitonin	Incstar	1: 500
Chromogranin A	Incstar	1: 500
CEA	Behring	1: 50
NSE	Innogenetics	1: 10
Phe 5	Enzo	1: 200
Bombesin (GRP)	Boehringer	1: 100
Synaptophysin	Sigma	1: 100
Somatostatin	Novo	1: 50
ACTH	Dakopatts	1: 500

Table 2 Immunohistochemical markers in three cases of mixed thyroid carcinomas (*T* tumour; *M* metastasis)

Antibody to	Case 1	Case 2 (T/M)	Case 3 (T/M)
Thyroglobulin	+(focal)	+/+	+/+
Calcitonin	+	+/+	–/–
Chromogranin A	+	+/+	+/+
CEA	+	+(focal)/+	+/+(focal)
NSE	+	+/+	–/–
Phe 5	+	+(focal)/+(focal)	–/–
Bombesin (GRP)	+	+/+	+(focal)/–
Synaptophysin	+(focal)	+/+	+/+(focal)
Somatostatin	–	–/–	–/–
ACTH	+	+/+	–/–

Results

In case 1 the nodule, 5 cm in diameter, was of hard consistency and seemed to consist of two partially confluent nodules without a distinct capsule. The cut surface was yellowish-white.

The major part of the tumour showed morphological features resembling a papillary carcinoma with predominant follicular and solid pattern (Fig. 1A), with focally well-defined branching papillae (Fig. 1B) resembling classical papillary carcinoma. We also found characteristic ground-glass nuclei and nuclear grooves as well as psammoma bodies. Within the papillary part of the tumour, which showed a focal positive reaction with antibodies against thyroglobulin, there was a circumscribed area with oxyphilic tumour cells. In addition, there were areas of medium-sized monomorphic tumour cells arranged in a solid pattern with pleomorphic nuclei embedded in an eosinophilic Congo red-positive ground substance, representing amyloid material (Fig. 1A). They were immunostained with antibodies to calcitonin (Fig. 1E), CEA, chromogranin A (Fig. 1D), bombesin, synaptophysin, Phe 5 and with anti-neuron-specific enolase (NSE) antibodies. In most areas the different tumour components were clearly separated, sometimes by a thin fibrous pseudocapsule (Fig. 1A). However, there were also small tumour cell clusters and single cells associated with the papillary component (Fig. 1C) which were positive for neuroendocrine markers (Fig. 1E). No reaction was observed with antibodies against somatostatin and adrenocorticotropic hormone (ACTH).

In case 2 each lobe of this "struma permagna" measured 10.5 cm in its greatest diameter. Most of the specimen was infiltrated by greyish-white and greyish-yellow hard nodular tumour masses. The tumour did not infiltrate beyond the fibrous capsule of the thryoid. In addition, nine lymph nodes, up to 2.5 cm in diameter, were removed.

The major part of the tumour showed solid areas consisting of medium-sized, slightly polymorphic cells with nuclei moderately rich in chromatin, which reacted strongly with antibodies to calcitonin, chromogranin A, NSE, CEA, Phe 5, ACTH, somatostatin and bombesin (Fig. 2C, E). The tumour cells did not react with antibodies to thyroglobulin and synaptophysin. In the right thyroid lobe, a small area of the tumour showed multiple follicular structures with ground-glass nuclei and nuclear grooves, exclusively positive for thyroglobulin (Fig. 2D). Foci with keratinizing squamous metaplasia (Fig. 2A, B) were interspersed. Follicular structures within the solid tumour component lacked the typical nuclear characteristics of papillary carcinoma (Fig. 2B). They also lacked thyroglobulin immunostaining (Fig. 2D) but reacted with antibodies to calcitonin and chromogranin A (Fig. 2E). Typical branching papillae were absent. Amyloid deposits were found focally within the tumour and its metastases. All lymph nodes contained tumour metastases resembling the medullary component; however, one lymph node was infiltrated by both tumour components (Fig. 2F, G).

In the third case, the biopsy was a greyish-white yellow nodule with sharp borders, 2.6 cm in largest diameter, close to the upper pole of the right thyroid lobe (Fig. 3A). Most of the resected lymph nodes were enlarged and showed a greyish-white cut surface.

The tumour contained a major follicular and papillary component with ground glass nuclei as well as a solid part with large eosinophilic and focally spindle-shaped cells. Furthermore, there was a papillary component with plump papillae with a homogeneous eosinophilic, Congo red-positive stroma (Fig. 3B). The nuclei of these tumour cells lacked a uniform ground-glass appearance. The two tumour components blended and the plump papillae were covered by both cell types (Fig. 3B). The solid tumour component and the cells covering the papillae eshowed a positive reaction with antibodies to chromogranin A, CEA, bombesin and synaptophysin (Fig. 3B). The other part of the tumour was only positive for thyroglobulin. We found chromogranin A- and CEA-positive cells in areas with predominant ground-glass nuclear features and nuclear grooves (Fig. 3C). The lymph node metastases showed both tumour components with marked predominance of the papillary type (Fig. 3D), but without plump, amyloid-containing papillae. They contained CEA- and chromogranin A-positive cells (Fig. 3D).

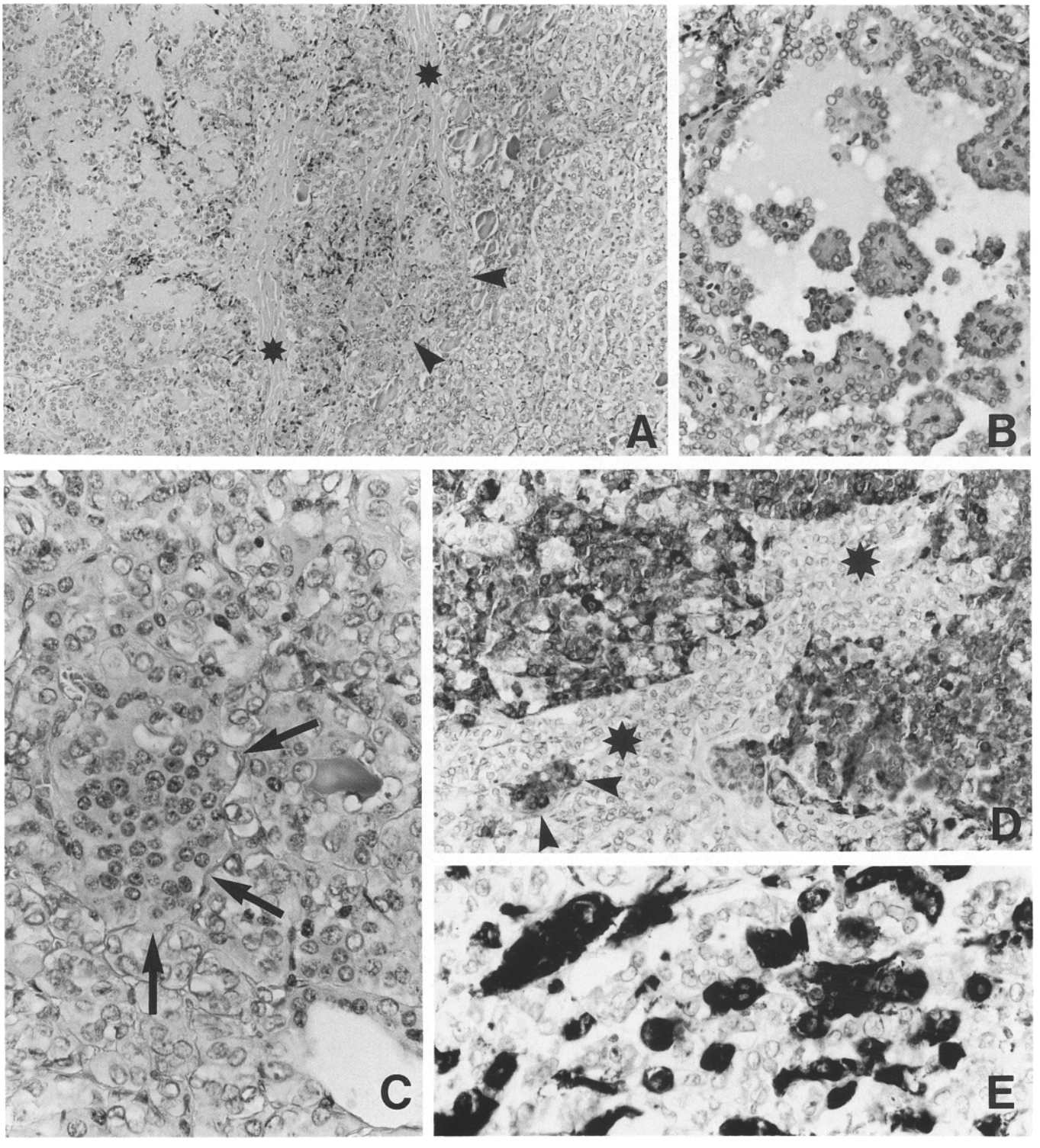
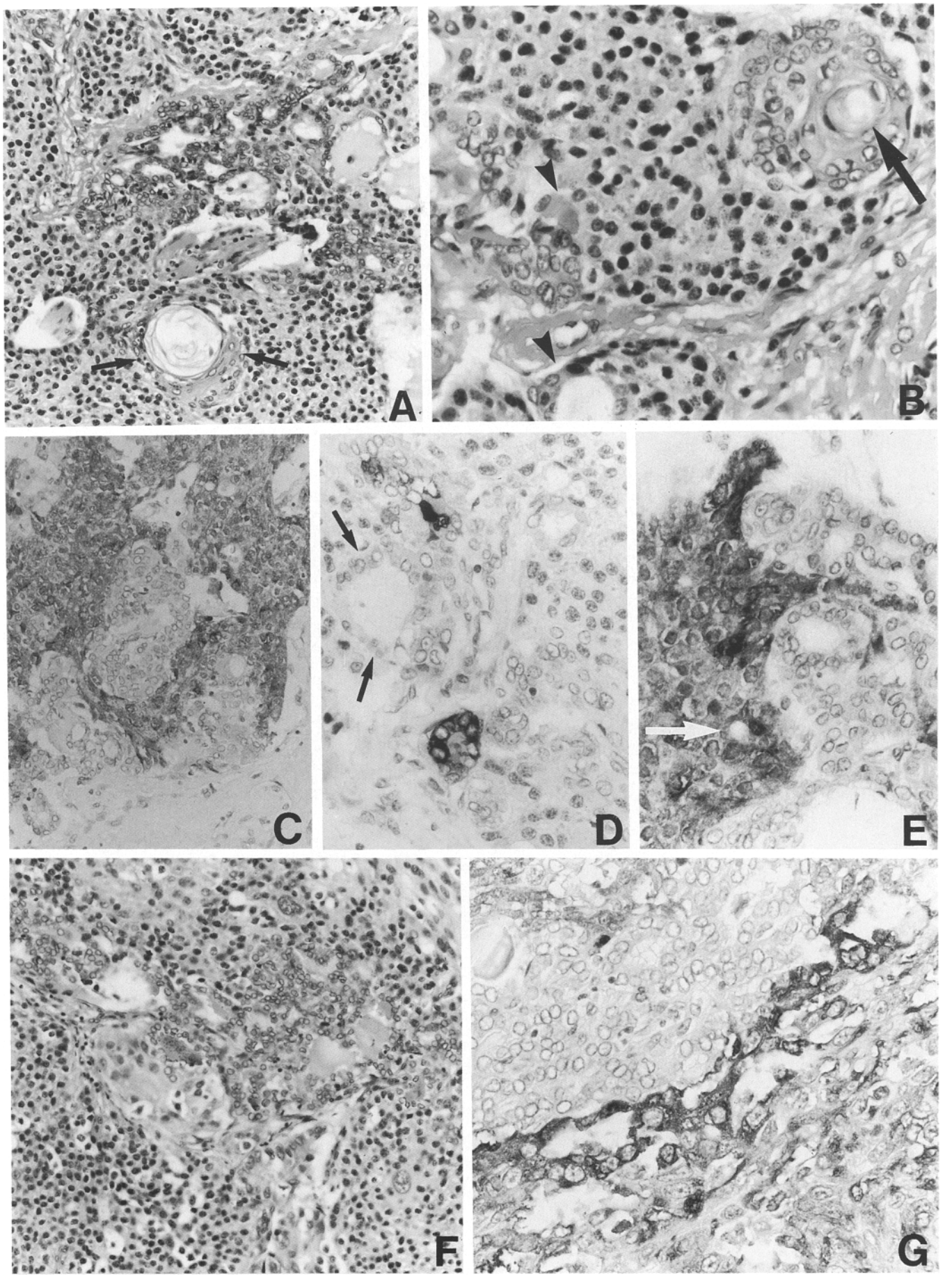


Fig. 1A–E Case 1. **A** Clear-cut borders between the tumour component with ground-glass nuclei (at the right) and that with medullary features. A small part of the medullary component (*arrowheads*) is lying beyond the thin fibrous capsule (*). Haematoxylin and eosin (H&E), × 40. **B** Classical papillae covered by cells with ground-glass nuclei close to the contact area, H&E × 100. **C** "Island" of the medullary component (*arrows*) surrounded by follicles and solid areas with ground-glass nuclei, H&E × 400. **D** Immunostaining [peroxidase-antiperoxidase (PAP) method] with antibodies to chromogranin A shows clear-cut borders between the two tumour components. One small nodule of the medullary component (*arrowheads*) is surrounded by follicles with ground-glass nuclei (*), × 100. **E** Small clusters and single cells with positive calcitonin-immunostaining (PAP method) within the papillary component close to the border to the medullary component, × 200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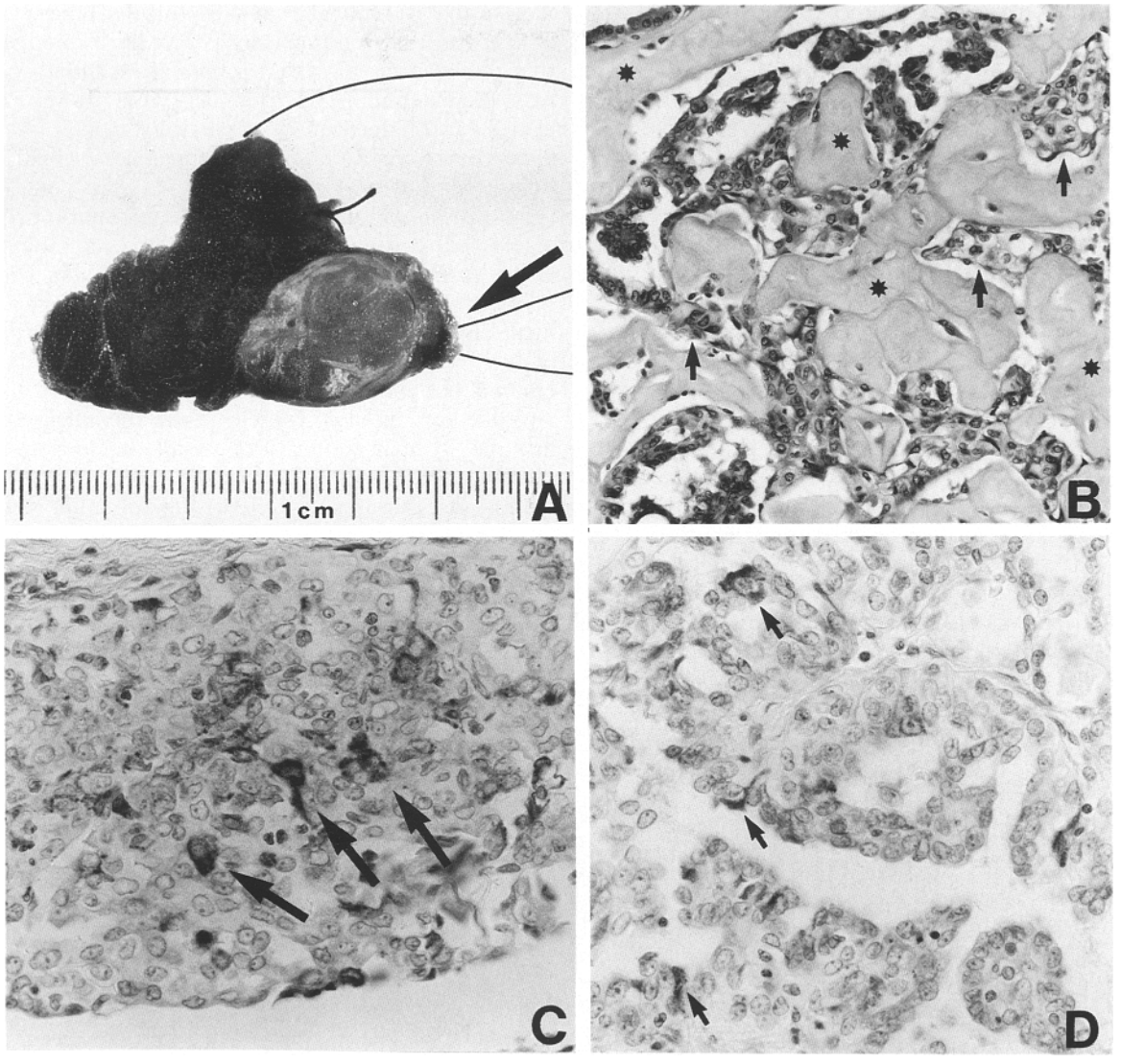

Fig. 3A–D Case 3. **A** Greyish-white to greyish-yellow nodule, 2.6 cm in its largest diameter, situated close to the upper pole (indicated by *arrow*) of the thyroid. **B** Plump papillae with amyloid (*) covered by chromogranin A-positive cells (PAP method) intermingled with chromogranin A-negative cells (*arrows*), ×200. **C** A solid area containing cells with predominance of ground-glass nuclei. Note focally positive immunostaining with carcinoembryonic antigen (CEA) antibodies (PAP method; *arrows*) ×400. **D** Few cells with positive CEA immunostaining (PAP method; *arrows*) in a tumour area showing predominant papillary features (lymph node metastasis), ×400

Fig. 2A–G Case 2. **A** Follicles consisting of cells with ground-glass nuclei within a solid tumour component. Note focus of keratinizing squamous metaplasia (*arrows*), H&E ×100. **B** Focus of squamous metaplasia (*arrow*) within the solid tumour component. Note follicles consisting of cells without ground-glass nuclei (*arrowheads*), H&E ×400. **C** Positive immunostaining with calcitonin antibodies (PAP method) confined to the predominantly solid tumour component containing cells without ground-glass nuclei, ×100. **D** Positive thyroglobulin immunostaining (PAP method) of follicular cells with ground-glass nuclei. Note lack of thyroglobulin immunostaining of the solid component and of follicles with cells without ground-glass nuclei (*arrows*), ×400. **E** Positive chromogranin A-immunostaining (PAP method) of the solid component containing one small follicle (*arrow*). The component with papillary nuclear features lacks immunoreactivity, ×400. **F** Both tumour components are present within a lymph node metastasis, H&E ×100. **G** The same chromogranin A-immunoreactive pattern (PAP method) as in Figure 2E is seen in the lymph node metastasis, ×400

Discussion

Comparison of the three thyroid tumours revealed common features as well as differences: all tumours showed a medullary component immunostained for calcitonin, chromogranin A and other neuroendocrine markers. They also contained tumour cell areas with ground-glass nuclei and nuclear grooves, which reacted with thyroglobulin antibodies. In case 1 distinct borders and a thin fibrous capsule existed between the two morphological

components. However, in the other tumours, and also the two tumours published by Albores-Saavedra et al. (1990), the two components were mixed. Consequently, the macroscopical aspect and the clear-cut borders between the two parts of tumour 1 at first glance favour collision of two separate tumours. Some contact areas, however, revealed a mixed pattern, which has not been observed in the few cases of coexisting medullary and papillary carcinoma reported by other authors (Ibanez et al. 1967; Justrabo et al. 1978; Lamberg et al. 1981; O'-Neil and Lomas 1984; Ishida et al. 1985; Gero et al. 1989). The morphological pattern closely resembled the mixed thyroid tumour published by Eusebi et al. (1990), with a smaller papillary and a larger oat-cell-like, calcitonin-free component, separated by clear-cut borders.

It is highly unlikely that tumours with a mixed pattern, also existing within the metastases, are the result of a collision of two different tumours. We assume that they arise from a common pluripotential precursor cell. This possibility has also been discussed by Ljungberg et al. (1983, 1984, 1992a), LiVolsi (1987), Albores-Saavedra et al. (1990) and Tanda et al. (1990). This assumption, however, apparently contradicts the recent postulate that follicular epithelium originates from the entodermal thyroglossal duct, whereas the ultimobranchial body contributes the C cells, originating from the neural crest (Pearse and Polak 1971). However, in support of this hypothesis, Williams et al. (1989) demonstrated C cells in thyroid glands lacking both lobes as a consequenc of a malformation of the "lateral thyroid anlage". Moreover, Pueblitz et al. (1993) found C cells within the thyroids of DiGeorge syndrome patients. A further supportive fact is the common presence of both C cells and thyroglobulin producing, follicle forming cells within solid cell nests (Harach 1985, 1987). Solid cell nests, first described by Getzowa (1907), have been regarded as remnants of the ultimobranchial body (Harach 1985, 1987, 1988; Ozaki 1991), because of the presence of C cells. A common origin of thyrocytes and C cells is also suggested by the fact that Kameda and Ikeda (1979) and Kameda et al. (1979) were able to isolate a thyroglobulin-like 27 S glycoprotein from human medullary thyroid carcinoma as well as canine C cells.

The features of tumours 2 and 3 and the observations reported by other authors strongly favour a common stem cell origin of C cells and thyrocytes. In tumour 2 with its predominantly solid pattern and focal follicular differentiation the lesion could be considered to be a "stem-cell carcinoma". Tumour 3 with its plump amyloid-containing papillae partially resembled the papillary variant of medullary carcinoma (Kakudo 1979; Rosai 1989). But in these areas we also found cells with ground-glass nuclei lacking immunostaining with the "neuroendocrine" antibodies used (Fig. 3B).

In the WHO classification of thyroid tumours (Hedinger et al. 1988, 1989) mixed medullary-follicular carcinomas are regarded as a variant of medullary carcinoma. A "real" mixed carcinoma consists of two components with different histological and adequate immunoreactive pattern in the primary tumour as well as in the metastasis. Tumours 2 and 3 fulfilled these criteria whereas in case 1 no metastasis had been removed. The first publications of mixed follicular-medullary carcinomas (Hales et al. 1982; Ljungberg et al. 1983; Pfaltz et al. 1983) stimulated many discussions. It is important to distinguish neoplastic from entrapped non-neoplastic follicles. Moreover, DeLellis et al. (1983) and Perrone (1986) discussed the possibility of absorption or phagocytosis of thyroglobulin by medullary carcinoma cells. Uribe et al. (1985) found a focal expression of thyroglobulin in 33.8% of 20 medullary carcinomas examined. Holm et al. (1987) demonstrated the coexpression of both thyroglobulin and calcitonin in a medullary carcinoma, but the thyroglobulin reactivity did not correlate with the formation of follicles; pure medullary carcinomas may contain follicle-like pseudoglandular structures (Hedinger et al. 1988). In tumour 2 the thyroglobulin immunostaining was restricted to the follicular structures with "papillary" nuclear features, whereas the others were only stained by antibodies to neuroendocrine markers. Eusebi et al. (1990) discussed a common stem cell origin of a compound oat-cell-like and papillary thyroid carcinoma, but they provided no information about the histological pattern of the lymph node metastases. Recently Ljungberg (1992a) also demonstrated cells with coexpression of both thyroglobulin and neuroendocrine markers within a group of predominantly solid tumours, which he called "thyroid carcinoma of the intermediate type".

It is further interesting, that no case of a real mixed thyroid carcinoma with papillary structures has been reported previously. The thyroglobulin-positive component always showed a follicular pattern, which led to the term "medullary-follicular" or "follicular-medullary" carcinoma. But the figures in the publications of Hales et al. (1982), Ljungberg et al. (1983), Pfaltz et al. (1983) and Tanda et al. (1990) also show ground-glass nuclei, typical of the follicular variant of papillary carcinoma. The biological behaviour and the lymphatic metastatic spread of the tumours described by Hales et al. (1982), Ljungberg et al. (1983), Pfaltz et al. (1983) and Tanda et al. (1990) are more typical of papillary carcinomas, since follicular carcinomas typically metastasize through the blood stream (Rosai 1989; Ljungberg 1992b). These facts support our opinion, that mixed thyroid carcinomas preferentially contain a papillary rather than a true follicular component. Moreover, mixed carcinomas can be recognized if the follicular component has nuclear features of papillary carcinoma. Medullary carcinomas with focal expression of thyroglobulin but without at least two different morphological components and mixed metastasis should not be called "mixed carcinomas". This view is also supportd by other authors (Ljungberg et al. 1983; Pfaltz et al. 1983; Perrone 1986; Holm et al. 1987).

Older reports of medullary carcinomas with an atypical pattern (Bussolati and Monga 1979) and with microfollicular structures (Valenta et al. 1977) exist. Normann et al. (1976) discussed diagnostic problems in medullary thyroid carcinomas with a mixed solid and so-called pseudofollicular or pseudopapillary growth pattern with

or without amyloid. But immunostaining with antibodies to thyroglobulin and neuroendocrine markers was not performed in these cases.

It is impossible to make a definitive statement concerning the prognosis of such combined thyroid carcinomas, few cases have been reported. Since all of our patients had metastases at the time of the operation or shortly afterwards and one patient died 3 years after the operation with diffuse metastatic disease, this could be regarded as indicator of high malignancy and poor prognosis. An unfavourable outcome has also been found in the group of thyroid carcinomas of intermediate cell type described by Ljungbreg (1992a). It is possible that some of the papillary carcinomas with a fatal outcome, especially those with a solid pattern reported by Tollefsen et al. (1964), were associated with a medullary component, which was not recognized at the time of investigation. Only cooperative studies of multiple centers with consequent long-term follow-up of patients with mixed thyroid tumours will provide useful prognostic information.

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