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Mixed medullary and follicular carcinoma of the thyroid

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Summary. We report a case of medullary carcinoma of the thyroid which on light microscopy showed not only the well known arrangement of cells in sheets and nests but also unequivocal follicular structures. These follicular structures are present both in the primary tumor and in lymph node metastases. Immunohistochemical investigations revealed that the cells lining the follicles produce thyroglobulin, whereas the remaining tumor tissue is positive for calcitonin and carcinoembrionic antigen. This case represents a medullary carcinoma of the thyroid with an atypical pattern consisting of both thyroglobulin and calcitonin producing cells.

Key words: Medullary carcinoma of the thyroid – Mixed medullary and follicular pattern

In 1959 Hazard et al. described medullary carcinoma of the thyroid (MCT) as a separate clinical and pathological entity and emphasized its solid nonfollicular growth pattern. Since then several large series of MCT have been reported in the literature (Freeman and Lindsay 1965; Gordon et al. 1973; Ibanez et al. 1967; Williams et al. 1966; Woolner 1971). All of these authors described the same basic histological picture of a tumor consisting of sheets and nests of small, undifferentiated cells. Woolner (1971) particularly stressed that variations in both the gross and microscopic appearance of MCT are much less than in follicular or papillary carcinomas of the thyroid. In contrast to these observations a case of thyroid carcinoma with a mixed medullary and follicular pattern has recently been reported in the literature (Hales et al. 1982). We report a case of MCT – presented already at the 3rd International Thyroid Symposium on Thyroid Cancer in Innsbruck in September 1982 – similar to the one published by Hales et al. in which

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Dedicated to Prof. K. Akazaki, Nagoya/Japan, on the occasion of his 80th birthday

the primary tumor and the lymph node metastases showed not only the well known arrangement of cells in sheets and nests, but also unequivocal follicular structures. Immunohistochemical investigation revealed that the cells lining these follicular structures produce thyroglobulin.

Materials and methods

Paraffin blocks of the primary tumor and of the lymph node metastases were available. Sections were stained with H&E, PAS, Masson-Trichrome, Elastic stain and Congo red. The immunohistochemical investigation for calcitonin was performed by a modified application of the unlabeled antibody-PAP method of Sternberger et al. 1970. Dilution of the goat anti-human calcitonin (kindly provided by Prof. Dr. J.A. Fischer, Orthopädische Universitätsklinik Balgrist, Zürich) was 1:1'280. The immunohistochemical investigation for thyroglobulin was also undertaken according to the method of Sternberger et al. 1970 and modified according to the technique described by Böcker and Dralle 1981. Dilution of the rabbit anti-human thyroglobulin (Henning, Berlin) was 1:400. All other antisera and the PAP complex were obtained from Cappell, Cochranville, PA. Negative controls were performed by substituting non-immune rabbit serum for the specific serum. In addition to these investigations a histoset of Immulok Inc., USA, was used to demonstrate production of carcinoembrionic antigen (CEA) by the tumor cells.

Case report

A 35-year-old man, who had been healthy prior to March 1982, presented with a swelling of the right laterocervical region. On physical examination thyroid cancer with lymph node metastasis was suspected. Right thyroidectomy with excision of cervical lymph nodes was performed on April 4th, 1982 in another hospital. Histology disclosed MCT with lymph node metastasis. The patient was referred to the University Hospital of Zürich for radical excision of the tumor. Left thyroidectomy was performed and submandibular, supraclavicular and mediastinal lymph nodes were removed.

Gross appearance

At operation, the right lobe of the thyroid gland ($5.0 \times 3.0 \times 3.0$ cm) including the pyramidal lobe ($2.0 \times 2.0 \times 1.0$ cm), were found to be involved by firm greyish-white tumor tissue and were resected. Several lymph nodes from the right side, also invaded by tumor tissue, were removed at that time. One month later one supraclavicular lymph node from the left ($2.1 \times 3.0 \times 5.0$ cm), two supraclavicular lymph nodes from the right ($3.5 \times 2.5 \times 2.0$ and $3.0 \times 3.0 \times 1.0$ cm), one submandibular lymph node from the right ($4.0 \times 2.5 \times 1.0$ cm) and a total of seven mediastinal lymph nodes of varying size were resected. All were firm and on cut surface yellowish-white to brown in colour. The left thyroidectomy specimen ($2.5 \times 2.0 \times 0.5$ cm) showed no lesions.

Microscopic appearance

Sections of the primary lesion show tumor surrounded by normofollicular thyroid tissue. The tumor is composed of broad columns and solid cell clusters of varying size (Fig. 1a). Occasionally follicular formations, some containing dark eosinophilic colloid, are present in the center of solid tumor. The neoplastic cells are spindle shaped or polygonal with lightly eosinophilic cytoplasm. Varying in size the nuclei are round or ovoid, some having very dense, dark, others coarsly granulated chromatin. Mitoses are rare. Broad bands of connective tissue and amyloid are present in the interstitium. Follicular structures present in these areas seem to correpond to thyroid tissue invaded by the tumor.

The histological picture of the metastases corresponds essentially to that of the primary tumor: follicular structures are present within clusters of solid tumor cells in all involved

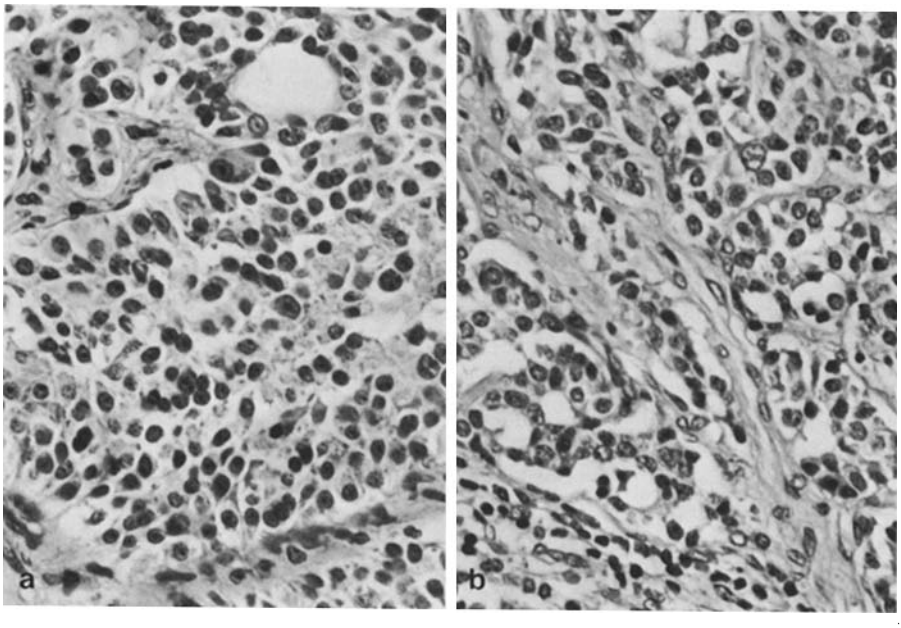

Fig. 1. a Medullary carcinoma of the thyroid with solid and follicular structures (H&E ×360). **b** Lymph node metastasis with follicular structure (H&E ×360)

lymph nodes, particularly in the submandibular and supraclavicular ones (Fig. 1b). The left thyroid lobe consists of normo- and macrofollicular, tumor free tissue.

Immunohistochemical results

Primary tumor

The tumor cells show a strongly positive reaction for calcitonin (Fig. 2a) and carcinoembrionic antigen (CEA) (Fig. 3a). With antithyroglobulin, the thyroid tissue surrounding the tumor, the thyroid follicles invaded by the tumor, as well as most of the follicular structures found within the solid sheets of tumor cells (Fig. 4a) give a strongly positive reaction.

Lymph node metastases

In all involved lymph nodes, the tumor tissue gives a strongly positive reaction for calcitonin (Fig. 2b) and CEA (Fig. 3b). With thyroglobulin, most cells lining the follicular structures and the colloid are found to be positive (Fig. 4b). Antithyroglobulin-positive follicular structures are more frequent in supraclavicular and in submandibular lymph nodes than in those from the mediastinum. Occasionally single tumor cells or solid groups of cells separate from follicular structures stain positively with antithyroglobulin.

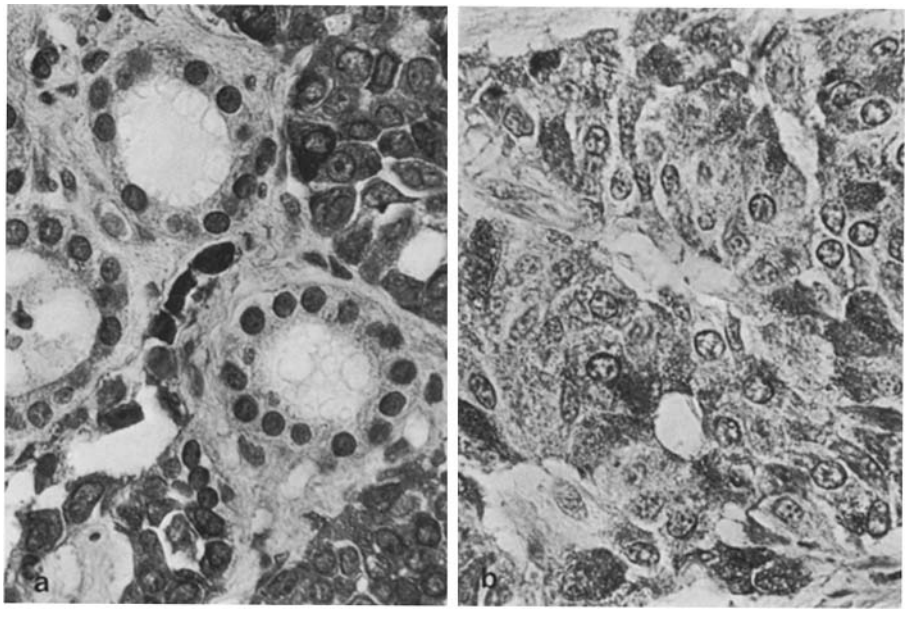

Fig. 2a, b. Immunohistochemical demonstration of calcitonin (× 560). **a** Primary tumor. **b** Lymph node metastasis

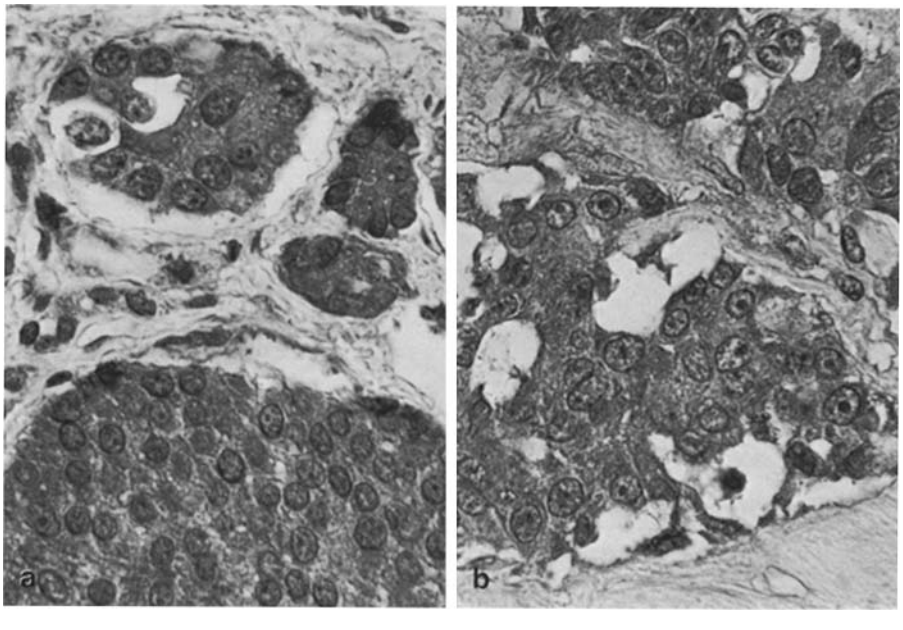

Fig. 3a, b. Immunohistochemical demonstration of CEA (× 560). **a** Primary tumor. **b** Lymph node metastasis

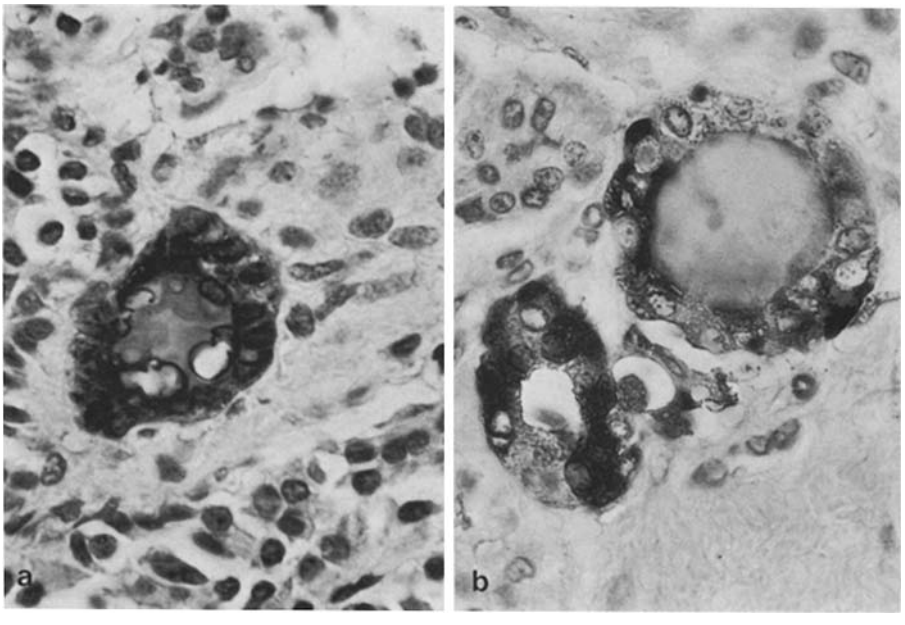

Fig. 4a, b. Immunohistochemical demonstration of thyroglobulin (× 560). **a** Primary tumor. **b** Lymph node metastasis

Discussion

The tumor described in this paper fulfills all criteria required for the diagnosis of MCT: arrangement of cells in sheets and nests, amyloid stroma and the production of calcitonin by tumor cells. In addition to these features the primary tumor and lymph node metastases show distinct follicular structures. In many cases of MCT follicular structures can be found between or even within the sheets of tumor cells. Since these tumors are surrounded by throid tissue, it is impossible to determine whether the follicles are part of the tumor or whether they represent thyroid tissue invaded by the tumor. In our case the presence of follicular structures within primary and metastatic lesions proves their origin from the tumor. Between 1977 and 1982 four cases of MCT with an atypical pattern similar to the one described above have been reported in the literature (Valenta et al. 1977; Bussolati and Monga 1979; Harach 1980; Hales et al. 1982). All four cases showed follicular structures either on light microscopy, or electronmicroscopic findings gave evidence for the follicular origin of at least part of the tumor cells. In one case (Valenta et al. 1977) poorly iodinated thyroglobulin but no calcitonin was shown to be produced by the tumor cells. The authors concluded that the tumor represents a follicular carcinoma with amyloid stroma. In two of the above mentioned cases (Bussolati and Monga 1979; Harach 1980) one was positive for calcitonin, the other for carcinoembryonic antigen. In neither of them were immunohistochemical investigations undertaken to demonstrate thyroglobulin production by the tumor cells. In the

case published by Hales et al. (1982), however, calcitonin and thyroglobulin positive cells have been demonstrated both in the primary tumor and in the metastases. Classical cases of MCT were investigated histochemically by Lo Gerfo et al. (1978), Burt and Goudie (1979) and Böcker et al. (1981) and biochemically by Ljunggren et al. (1973) for the production of thyroglobulin by the tumor cells. None of their cases – including three of metastasizing MCT – were found to be positive. In our case – similar to the one described by Hales et al. (1982) – the primary tumor as well as the lymph node metastases are positive for calcitonin. In contrast, the follicular structures found within the nests of calcitonin producing tumor cells are positive for thyroglobulin. These findings confirm the existence of atypical cases of MCT and give further evidence of the existence of mixed tumors consisting of both calcitonin and thyroglobulin producing cells. This agrees well with the fact that occasional regression of tumor growth can be achieved by triiodo-thyronin treatment in patients with MCT (Wahner et al. 1968; Didolkar and Moore 1974). We believe that thyroid tumors of mainly trabecular pattern should be investigated more often by immunohistochemical means – even in the absence of an amyloid stroma. The incidence of atypical MCT is likely to be higher than the few cases reported in the literature to date would indicate.

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