Virchows Arch [Pathol Anat] (1983) 400:61–67

Virchows Archiv A

Anaplastic type of medullary thyroid carcinoma

An ultrastructural and immunohistochemical study

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Summary. A case of anaplastic type of medullary thyroid carcinoma is presented. Immunoperoxidase study revealed calcitonin within the tumor cells, which also showed argyrophilia. At ultrastructural examination the tumor also displayed mucoid and squamous differentiation.

This multidirectional differentiation (endocrine and exocrine) underlies the difficulty of ascribing a precise histogenesis to this tumor.

Key words: Thyroid – Anaplastic carcinoma – Medullary carcinoma

Medullary thyroid carcinoma (MTC) is a clinico-pathologic entity, histologically characterized by a solid proliferation of round/oval/spindle neoplastic cells, amyloid deposition in the stroma and clinically characterized by a fairly good prognosis. The tumor cells produce calcitonin which can be demonstrated immunohistochemically. Recently some cases of anaplastic variants of medullary thyroid carcinoma (AMTC) have been reported (Kakudo et al. 1978; Mendelsohn et al. 1980; Nieuwenhuijzen Kruseman et al. 1982). A new case is described here which increases the morphological and histogenetic knowledge of this tumor.

Case report

A 56 year-old woman was admitted to the Policlinico S. Orsola, Bologna University, in September 1980. The patient showed diffuse neoplastic enlargement of the thyroid gland. Plasma calcitonin level was not elevated and no hormonal syndrome was detected. The patient underwent partial thyroidectomy because of tumor extension to the adjacent surrounding cervical tissues. The incompletely removed tumor mass measured $3.5 \times 2.5 \times 2$ cm. Immediately after surgery a tracheotomy was performed because of tracheo-malacia. Subsequently the patient developed repeated episodes of broncho-pneumonia. Her health grew progressively worse and she died two months after surgery. An autopsy was not performed.

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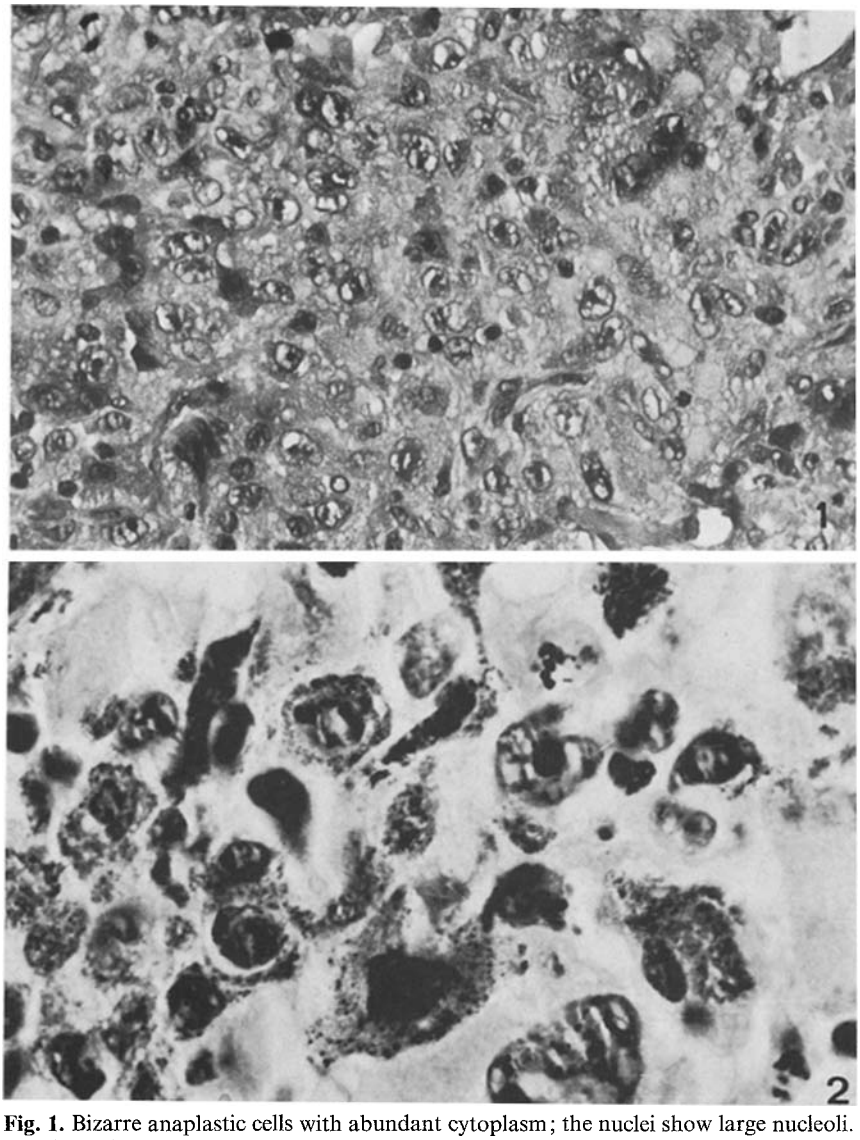

Fig. 1. Bizarre anaplastic cells with abundant cytoplasm; the nuclei show large nucleoli. Hematoxylin-eosin, × 330

Fig. 2. Argyrophilic granules in the cytoplasm of tumor cells. Bodian silver impregnation, × 1,056

Materials and methods

Sections of Carson-fixed, paraffin-embedded thyroid tissue were stained according to the following methods: H.E.; PAS with and without diastase pre-treatment; Alcian-blue (pH 2.5); Congo red stain; PTAH; Masson's trichrome; Grimelius; Bodian and Masson-Fontana. An immunoperoxidase method (Bussolati and Monga 1979) using anti-calcitonin antiserum (kindly supplied by Prof. G. Bussolati) was used.

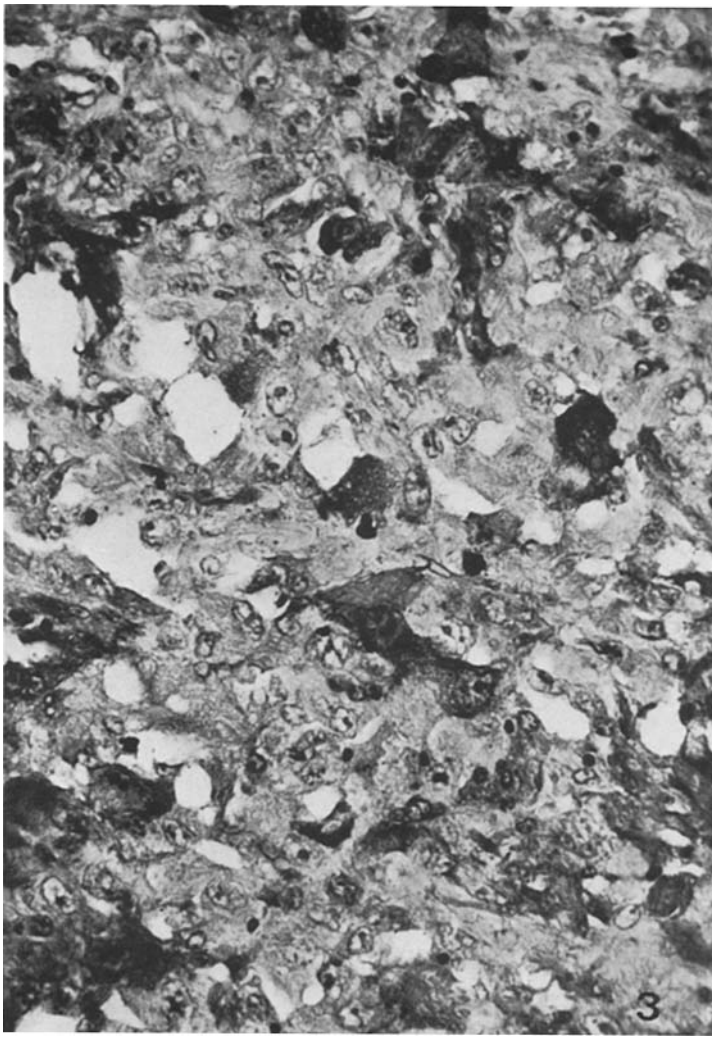

Fig. 3. Positive immunoperoxidase stain for calcitonin in tumor cells, × 423

For purpose of electron microscopy some Carson-fixed blocks were post-fixed in 1% osmium tetroxide and embedded in epoxy resin (Araldite). Ultrathin sections were stained with uranyl acetate-lead citrate.

Light microscopy reveals a solid and highly malignant anaplastic neoplasm (Fig. 1). The tumor cells are large and undifferentiated: giant, fusiform and rare multinucleated elements are observed. Cytoplasm is abundant, vacuolated and sometimes eosinophilic. The nuclei are polymorphic and show distinct nucleoli. Nuclear inclusion bodies are also seen and atypical mitoses are common. Intracytoplasmic alcianophilic vacuoles are observed as well as PAS positive granules. The Congo red stain is negative. Argyrophil granules as well as the presence of calcitonin are immunohistochemically documented in some anaplastic cells (Figs. 2, 3).

Electron microscopy. On electron microscopy the tumor is composed of anaplastic cells. The grade of cohesion of tumor elements varies in different fields. The neoplastic cells show plasma

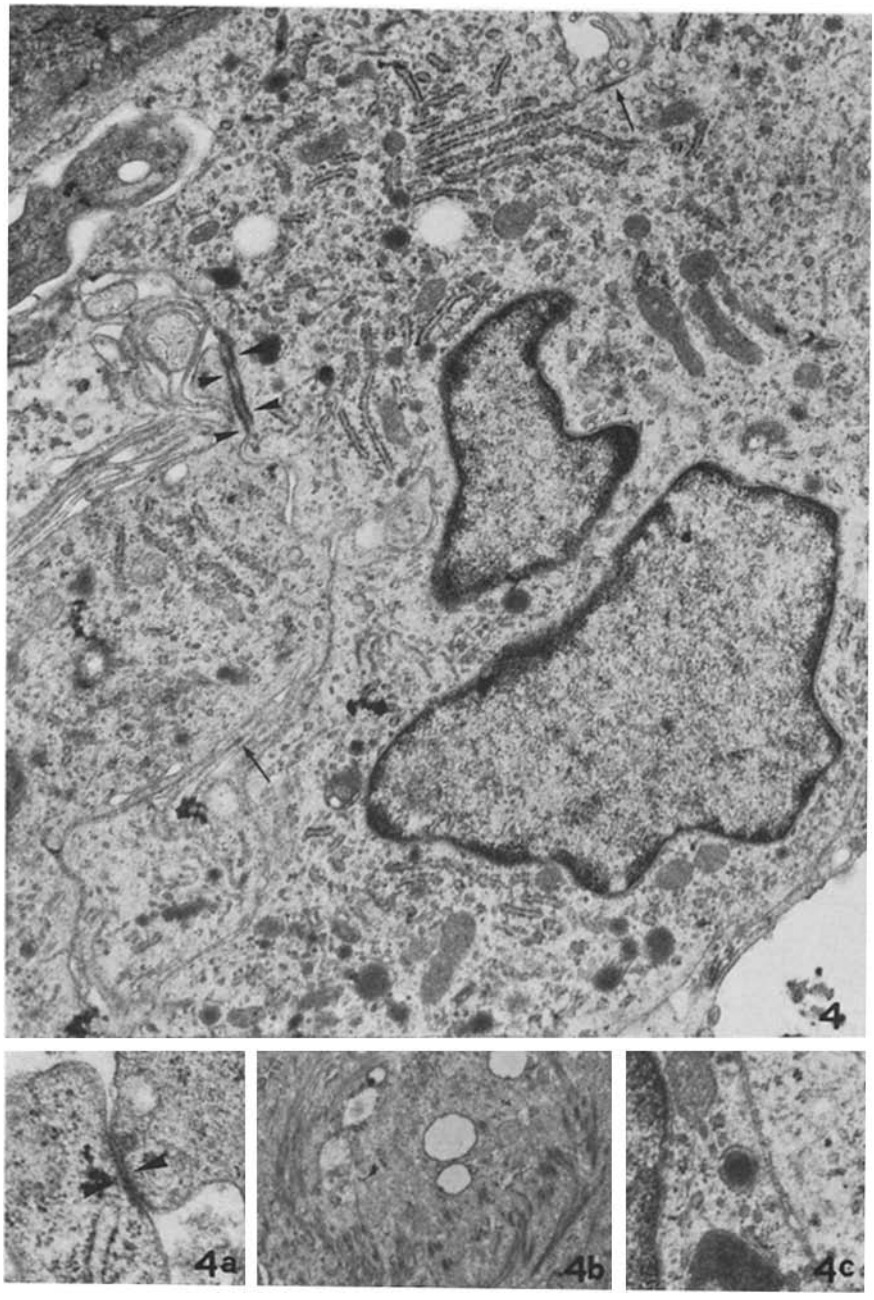

Fig. 4. Interdigitations join adjacent cells focally locked also by desmosome-like structures (*arrow*) and/or by rare long junction-like formations (*arrow-heads*). Scattered and/or clustered neurosecretory-type granules are present in the cytoplasm (×15,000). *Inset a:* leaky tight junction-like structure (×35,000). Inset b: swirl of closely-packed tonofilaments (×6,850). *Inset c:* a dense-core neurosecretory-type granule (×15,000)

membranes which are generally parallel and smooth. Alternatively, their surface is more irregular with some cytoplasmic extrusions, and cellular locking by interdigitations is frequently observed (Fig. 4). The cells are rarely joined by small inconspicuous or attenuated desmosome-like structures and/or small membrane densities similar to leaky tight junctions (Fig. 4, inset a). The nuclei are irregular with deep invaginations of the nuclear envelope. Enlarged, sometimes marginated, nucleoli are found. Sparse multinucleated cells are also present. In many cells the cytoplasm contains markedly dilated rough endoplasmic reticulum as well as moderately developed Golgi zones.

Characteristically most of the tumor cells displays a varying number of scattered dense-core neurosecretory-type granules of different diameters, ranging from 100 nm to 250 nm (Fig. 4). In some tumor cells, in addition to neurosecretory-type granules, mucin-like vacuoles containing an electron-lucent matrix with eccentric electron-dense spherules are observed. In some instances they appear entrapped in prominent swirls of closely-packed microfilaments resembling tonofilaments (Fig. 4, inset b). The hyaloplasm contains abundant free ribosomes and polyribosomes, lipid droplets, and rare collections of glycogen particles. Sparse tumor cells lacking in neurosecretory-type granules are characterized by a less electron-dense microfilament-laden cytoplasm, and by an eccentricallly placed nucleus. Condensation of microfilaments into more electron-dense parallel bundles of tonofilaments adjacent to clustered mucin-like vacuoles occurs generally at the cell periphery. Occasionally an often incomplete basal lamina, investing the outer face of the neoplastic cell membranes is observed.

Discussion

The light and histochemical findings of our case are similar to those recently observed by some authors in anaplastic variants of medullary thyroid carcinoma (AMTC) (Kakudo et al. 1978; Mendelsohn et al. 1980; Nieuwenhuijzen Kruseman et al. 1982). In the literature, previous reports of medullary thyroid carcinoma (MTC) with anaplastic areas or showing nuclear atypias have also been described (Williams 1968; Nishiyama et al. 1972; Zeman et al. 1978; Bussolati and Monga 1979). When MTC shows anaplastic changes, the neoplasm may show aggressive behavior suggesting transformation from low to high-grade malignancy. Therefore it appears that it should be differentiated from the typical MTC which generally has a good prognosis (Hazard et al. 1959). AMTC should also be distinguished from an anaplastic giant-type, non-medullary carcinoma of the thyroid.

The exact diagnosis has an important clinical significance because of the possible familial occurrence of MTC. When examined with light and electron microscopy, the two tumor forms show a number of morphological similarities (Meissner and Warren 1969; Gaal et al. 1975; Jao and Gould 1975; Valenta and Michel-Béchet 1977; Johannessen et al. 1978; Newland et al. 1981), and even the demonstration of "neurosecretory granules" cannot be decisive in the differential diagnosis. In fact neuroendocrine-like structures have also been observed in non-medullary thyroid carcinoma (Cameron et al. 1975; Jao and Gould 1975; Valenta and Michel-Béchet 1977; Valenta et al. 1977; Johannessen et al. 1978).

The presence in medullary tumors of argyrophil granules, in addition to the positivity of calcitonin reaction in the cytoplasm of tumor cells, are features of undisputed diagnostic value. Due to the presence of both of these histochemical findings the case reported here can be regarded as medullary differentiation of an anaplastic thyroid carcinoma. However the ultrastructural examination of our case showed, in addition to the neurosec-

retory granules, features of mucoid and squamous differentiation which is not to be expected in tumors derived from C-cells. Therefore we think that two histogenetic hypotheses can be proposed. The neoplasm may represent a true epithelial tumor (dedifferentiated follicular carcinoma) with ectopic production of calcitonin (Calmettes et al. 1982). The second possibility is that, according to Gould et al. (1981), these findings can be explained with the phenomenon of the "multidirectional differentiation", occurring as the result of poorly understood microenvironmental factors (Sidhu 1979). The presence of such mixed phenotypes in neoplasms of known neural crest group origin suggests that rigidly equating certain neoplastic cellular structures with a given histogenetic derivation may not be correct. Instead these observations further strengthen the hypothesis of "multidirectional differentiation" that cut across the boundaries of the three primitive embryonic layers (Gould et al. 1981).

Acknowledgements. The authors wish to thank Prof. J.G. Azzopardi for his critical evaluation of the manuscript.

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Accepted February 7, 1983