ANIMAL MODEL OF HUMAN DISEASE

Medullary Thyroid Carcinoma, Multiple Endocrine Neoplasia, Sipple's Syndrome

Animal Model: Ultimobranchial Thyroid Neoplasm in the Bull

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Biologic Features

A syndrome of ultimobranchial thyroid neoplasms which shares many similarities with medullary thyroid carcinoma of man occurs frequently in populations of aged bulls. Jubb and McEntee[1] reported that approximately 30% of bulls had neoplasms and an additional 15 to 20% had hyperplasia of ultimobranchial derivatives. These disturbances of growth have been found only in thyroid glands of bulls but not cows.

Ultimobranchial adenomas have been encountered more frequently than carcinomas in bulls.[1,2] Adenomas usually were well circumscribed and situated near the hilus of the thyroid. Ultimobranchial carcinomas were larger and ofter caused observable enlargements in the anterior cervical region. They completely incorporated the thyroids and metastatized to the cervical lymph nodes and lung (Figure 1). The cells comprising adenomas had a lightly eosinophilic cytoplasm and either were arranged into small groups or formed ductal and acinar structures. Carcinomas were composed of solid nests of polyhedral to spindle-shaped cells with occasional mitotic figures.

Ultrastructurally, the most characteristic cell type in ultimobranchial neoplasms had large aggregations of concentric or interwoven microfilaments which often partially indented the nucleus (Figure 2). Secretion granules were membrane-limited, composed of fine dense particles and appeared similar to those in normal parafollicular (C) cells of control bulls.[3] Studies by Pearse *et al*[4] suggest that the formation of fine protein microfilaments is one of the distinctive characteristics of C cells and other polypeptide-hormone secreting cells of the APUD (amine, precursor uptake, decarboxylase) series. Other neoplastic cells were polyhedral and appeared to be poorly differentiated. The small cytoplasmic area contained clusters of free ribosomes, prominent Golgi apparatuses and mitochondria but few secretion granules. Ultimobranchial

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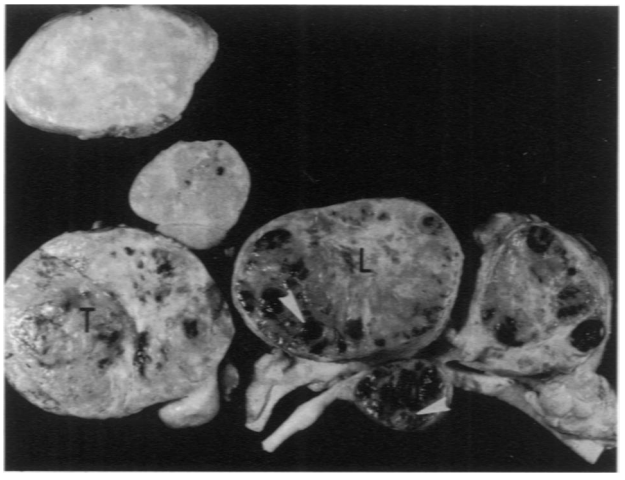

Fig 1—Ultimobranchial thyroid carcinoma in a bull with metastases in several cervical lymph nodes. Neoplastic tissue has completely incorporated the thyroid gland (*T*) and metastases in cervical lymph nodes (*L*) form large firm masses with areas of necrosis and hemorrhage (*arrowheads*).

tumors were firm, and large aggregations of fine amyloid fibrils often were observed between bundles of collagen fibers.

Bioassay of ultimobranchial adenomas and carcinomas demonstrated the presence of calcitonin activity (466 ± 84 and 409 ± 93 MRC mU/g, respectively),[2] and calcitonin has been detected at higher than normal levels in plasma of bulls by immunoassay.[5] Calcium infusion to raise serum calcium to 12.6 ± 0.6 mg/100 ml increased plasma calcitonin-like activity 210 ± 31% above preinfusion levels after 1 hour.[2] Mean serum calcium in 15 bulls with calcitonin-secreting thyroid tumors (9.51 mg/100 ml) was slightly lower than in 20 adult controls (9.92 ±0.2 mg/100 ml).

Parathyroid glands from bulls with ultimobranchial neoplasms had ultrastructural evidence of secretory inactivity and atrophy of chief cells. Cytoplasmic organelles were poorly developed, and secretion granules were infrequent. The large cytoplasmic area had numerous lipofuscin granules and cytosegresomes. Parathyroid hyperplasia and adenomas, reported in patients with familial medullary thyroid carcinoma, have not been observed in bulls. Prominent aggregations of amyloid fibrils occasionally were observed around the inactive chief cells.

The etiology of the localized amyloid deposition in parathyroid glands and thyroid neoplasms with this syndrome is uncertain, but it is not associated with chronic suppurative lesions in other organs. Amyloid production is consistently associated with medullary thyroid carcinoma in man and also has been reported in other endocrine tumors. Chemical differences exist between amyloid fibrils of immunoglobulin origin and those produced by endocrine tumors.[6]

Vertebral osteosclerosis with ankylosing spondylosis deformans and degenerative osteoarthrosis often are detected coincidentally in bulls with ultimobranchial tumors.[2] Skeletal lesions of this type have been

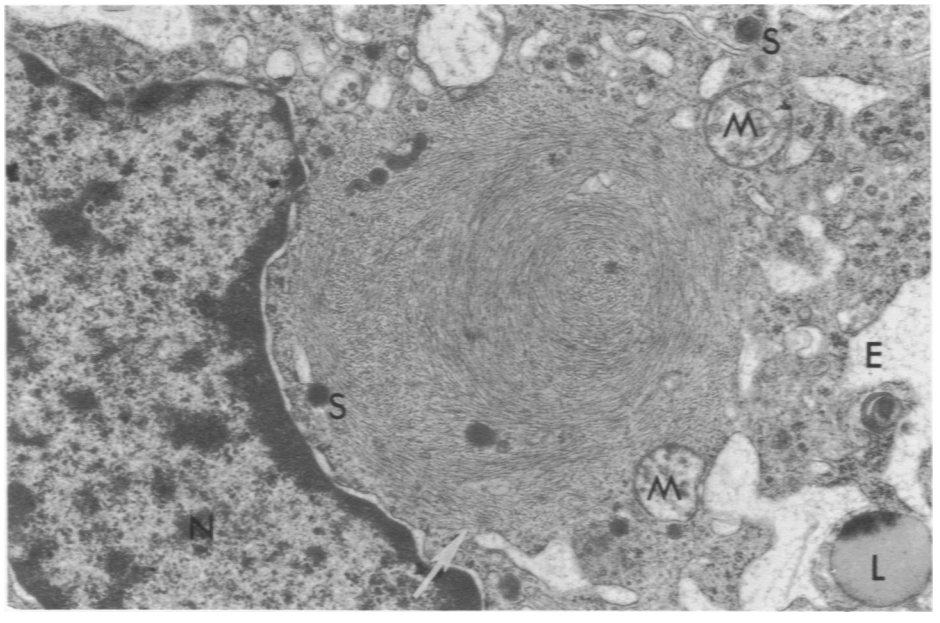

Fig 2—Cell from an ultimobranchial adenoma illustrating the distinctive aggregations of interwoven microfilaments (*arrow*) which frequently indent the nucleus (*N*). Membrane-limited secretion granules (*S*) are scattered between the network of microfilaments and elsewhere in the cytoplasm. Large mitochondria (*M*), distended profiles of endoplasmic reticulum (*E*), clusters of ribosomes and lipofuscin (*L*) granules are present (X 20,300).

reported to occur frequently in adult bulls but are rare in cows of the same age and breed.[7] The relationship of excessive calcitonin secretion to the pathogenesis of the skeletal lesions currently is uncertain and requires additional investigation. Prominent bone lesions have not been reported in patients with medullary thyroid carcinoma.[8] Multiple endocrine tumors (bilateral pheochromocytomas and pituitary adenomas) were detected in bulls with ultimobranchial neoplasms as has been reported in patients with medullary thyroid carcinoma.[8]

Comparison with Human Disease

Medullary thyroid carcinoma in man and ultimobranchial neoplasms of bulls both appear to be derived from parafollicular (C) cells, have an amyloid stroma, contain calcitonin which can be released by calcium infusion, and are associated with a syndrome of multiple endocrine neoplasia. Cells comprising medullary thyroid carcinoma are more differentiated and have well-developed organelles and numerous secretion granules. The higher levels of calcitonin reported in medullary carcinomas of man than in bulls was interpreted to be a reflection of the degree of differentiation of neoplastic cells.

A possible relationship has been suggested between the long-term dietary intake of excessive calcium and the high incidence of ultimo-

branchial neoplasia in bulls. Krook *et al*[9] reported that adult bulls frequently ingest from 3.5 to 5.9 times the amount of calcium normally recommended for maintenance. The chronic stimulation of ultimobranchial derivatives by high levels of calcium absorbed from the digestive tract may be related to the pathogenesis of the neoplasms. Cows do not appear to develop ultimobranchial lesions under similar dietary conditions, possibly because of the high physiologic requirements for calcium imposed by pregnancy and lactation.

Usefulness of this Model

Since the animal model shares many important characteristics with the human disease, it offers a unique opportunity to investigate the long-term effects of excessive calcitonin secretion on calcium homeostatic mechanisms and bone metabolism. Investigations with this animal model may help to further define the physiologic role of calcitonin and its interaction with parathyroid hormone in the pathogenesis of certain metabolic diseases.

Availability

The frequent occurrence of ultimobranchial tumors in aged bulls and the large populations of bulls maintained at artificial insemination centers in several regions of the United States provide a source of animals with this syndrome.

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