Editorial

Branchial and Thymic Remnants in the Thyroid and Cervical Region: An Explanation for Unusual Tumors and Microscopic Curiosities

In this issue, Mizukami et al. [25] describe incidentally found ectopic thymus in the thyroid of a patient with Graves' disease. The thymic tissue composed of lymphoid cells admixed with Hassell's corpuscles was found in an interlobular septum of the thyroid.

The presence of thymic tissue in the thyroid gland is unusual; most ectopic thymus is found in or at the thyroid capsule or within the perithyroidal soft tissue. Developmental and embryological events can explain the presence of thymic tissue in the neck and in the thyroid gland.

The median anlage of the thyroid arises as a bilobated vesicular structure at the foramen cecum of the tongue; it is attached to the tongue by the thyroglossal duct [1, 27, 32, 36]. In the ninth week of fetal life, the solid thyroid differentiates into cords and plates a few cells thick. Follicles develop at approximately the 10th week of gestation as bead-like enlargements arise along the cords throughout the gland and tiny lumens appear. At 12 weeks' gestation, colloid formation begins.

The lateral thyroid, which fuses with the median anlage, develops from branchial tissues. Dispute has arisen among embryologists as to the number of branchial pouches present during human fetal development. Norris [28] believed that in human fetal development, only 4 pouches can be recognized and that the lateral thyroid is derived from the caudal end of the fourth branchial pouch.

Other authors extrapolate from the embryological studies of other animals and use the term *ultimobranchial body* for the fifth branchial pouch, which gives rise to the lateral thyroid [33]; it is debated whether the caudal end of the fourth pouch represents the fifth branchial pouch or not. Sugiyama [32] refers to "the fourth-fifth branchial pouch complex."

In the human fetus, the lateral anlage of the thyroid is derived from the fifth (or tail of the fourth) branchial pouch or ultimobranchial body. The latter, still connected to the pharynx, gradually loses this connection in the seventh week of life. Its lumen is obliterated by proliferating cells and it appears as a solid mass surrounding the median thyroid tissue. The ultimobranchial bodies give rise to C cells.

In addition to C cells, some authors believe that the lateral anlagen gives rise to structures indistinguishable from follicles [28]. Hence, cords of cells from the medial thyroid migrate and enwrap themselves around the solid ultimobranchial body. Fusion occurs between the 2 anlagen and follicles develop. Whether some of these follicles are actually of lateral anlage derivation is unclear.

In humans with thyroid nondescent (or unilateral aplasia) [17], there are no recognizable thyroid follicles in these usual locations. It appears unlikely that the ultimobranchial body alone contributes to thyroid follicle development. It still may be possible, however, that specific interactions between medial and lateral anlagen could lead to an ultimobranchial component to thyroid follicles.

Sugiyama's studies [32] indicate that the ultimobranchial body, after it fuses with the medial thyroid, divides into a central thick-walled, stratified epithelial cyst and a peripheral part composed of cell groups dispersed among follicles—C cells. In postnatal life, the central epithelial cyst may disappear. It corresponds to so called solid cell nests [18, 19, 32]. Estimates of the relative contributions to thyroid weight from the lateral anlagen range from less than 10 to 30 percent of total thyroid weight [28, 33, 36].

In rare instances when the ultimobranchial body remnants fail to fuse with the medial thyroid, nests of solid and cystic squamous-appearing cells associated with

lymphocytes may be found in the neck [19, 32, 33]. In avian species, this is the normal pattern of development [18]. When development of the third and fourth branchial pouches is arrested, parathyroids, thymus, and C cells are absent (DiGeorge syndrome) [6].

Because the thyroid develops in conjunction with the branchial or pharyngeal pouches, derivatives of these structures can sometimes be found in the gland. Intrathyroidal parathyroid tissue, salivary gland remnants, and thymic tissue can be seen [7, 10, 18, 26, 36]. Solid cells nests, representing nests of the ultimobranchial bodies, have been reported in 21–89% of human thyroids [12, 14, 37].

Branchial and thymic tissue in the thyroid is usually an incidental microscopic finding and is rarely of clinical significance. However, on rare occasions, such remnants may enlarge, become cystic, or purportedly undergo neoplastic transformation. These lesions can be explained on the basis of embryology; although rare, they comprise an interesting group of thyroid nodules with diverse biology. These lesions can be divided into neoplastic and nonneoplastic groups.

Neoplasms

Ectopic Cervical Thymomas

Histologically, classic thymomas may occur in the thyroid or in perithyroidal tissues; many of the latter present as and mimic intrathyroidal masses because of their location [23, 34]. Sixteen patients with ectopic cervical thymoma were accepted by Chan and Rosai in their review [9], and one additional patient has been published [34]. Of these 17 patients, 15 were women; all were adults (average age, 44 yr). Seven tumors were described as near the lower end of the thyroid, 6 in soft tissues near the thyroid and 3 within the gland. Three of these tumors was considered at least microscopically invasive, although most were benign histologically and clinically.

Ectopic Hamartomatous Thymomas

These unusual lesions, which occur in the lower neck and not in the thyroid, are mentioned for completeness as part of the spectrum of branchial remnant—related lesions that can occur in the neck [9, 11, 15, 16, 29, 30]. These circumscribed masses are composed histologically of spindle cells, epithelial nests, and fat. Muscle cells have also been described [30]. These are benign lesions.

SETTLE (Spindle Epithelial Tumor with Thymus-like Differentiation)

This unusual intrathyroidal lesion is composed of spindle cells and some epithelioid clusters; they resemble synovial sarcomas [9]. All of the 8 patients reported were diagnosed under 25 years of age. The sex distribution was approximately equal. The biology of these lesions is one of indolent biological behavior; metastases to regional nodes and lungs occur late in the course of the disease (6–22 yr).

The differential diagnosis includes medullary carcinomas of the thyroid and synovial sarcomas. The former are distinguished by absence of staining for chromogranin, calcitonin, and calcitonin gene—related peptide. The latter, which have not been defined as intrathyroidal tumors are distinguished because spindle cells are nonepithelial. In SETTLE, both the recognizable epithelial elements and the spindle-cell component are keratin-positive and show epithelial characteristics by electron microscopy.

CASTLE (Carcinoma Showing Thymus-like Differentiation; Squamous-cell Carcinoma of the Thyroid)

CASTLE are malignant tumors of the thyroid or perithyroidal tissues [2, 9, 10, 20, 24]. Of the 12 reported patients, 10 had intrathyroidal tumors, and 2 tumors occurred in the soft tissues of the upper neck. All patients were adults (age range; 25–69 yr; 8 women, 4 men). These are invasive, often large, tumors that replace entire thyroid lobes or extend over large areas of the thyroid. The biological behavior is that of carcinomas; local recurrences, distant metastases, or both, were identified in half the patients reported.

Some of these lesion have been classi-

fied in the literature as malignant teratomas of the thyroid in adults [9] or as anaplastic thyroid carcinomas [2].

Sclerosing Mucoepidermoid Carcinomas with Eosinophilia

This unusual entity, described in 1991 by Chan et al. [8] consists of an infiltrating tumor occurring in the background of chronic lymphocytic thyroiditis. The lesion is composed of strands and nests of epidermoid cells encased in a dense fibrous stroma. Focally definite squamous differentiation is noted. Small pools of mucin are found in 75% of patients. An extensive eosinophilic leucocyte infiltration is found in all patients. The tumors do not contain either thyroglobulin or calcitonin; they are strongly immunoreactive for cytokeratin. It has been suggested that these lesions may be derived from solid cell nests [16].

Despite the infiltrative nature of this tumor—extension beyond the confines of the thyroid capsule and even regional node metastases—the biological behavior is indolent; with local recurrence developed in 1 of 5 patients (in whom sufficient follow-up was available).

Non-neoplastic

Thymic Tissue

Damiani et al. [10] reported finding thymic rests in 1.4% of more than 2,000 thyroid glands studied. Neill [26] illustrated an entire thymus gland within the thyroid of an autopsied infant. von Domarus and Blaha [35] reviewed the reported patients with ectopic thymus in the neck and found 68 were acceptable; they added 1 additional patient. Although these thymus glands can appear entirely normal, many show cystic change and clinically present as cystic neck masses.

Microscopic cervical thymic remnants are very common and are often seen admixed with parathyroid tissue in surgical specimens from neck explorations. Barr et al. [3] noted dermal thymic rests in the necks of 2 children who also demonstrated congenital anomalies in the head and neck area.

Solid Cell Nests

Solid cell nests (SCNS) are not an uncommon finding in the posterolateral or posteromedial portion of the lateral lobes of the thyroid [31]. They can be found in up to 21% of glands and in 33–89% of fetal/neonatal glands [4, 13, 16, 19, 37]. These nests are composed of epidermoid cells with palisading at the edges of the nests [16]; occasionally, cysts will be formed. Mucin may be found in some of these SCN cells. Most authors believe these SCNs represent rests of ultimobranchial body [19, 31]. C cells immunoreactive for calcitonin, near or within solid cell nests, seem to be evidence of such a relationship [12, 14, 19].

In chronic lymphocytic thyroiditis, especially the fibrous variant, these SCN become quite prominent [19]. In 2 reported patients, associated C-cell hyperplasia was found in lymphocytic thyroiditis [5, 21]; the association of C cells with ultimobranchial body rests and the further finding of C-cell hyperplasia in thyroiditis (in which UBB hyperplasia is known to occur) point to a significant relationship among these entities. The role of thyrotropin-stimulating hormone (TSH) (which is elevated in hypothyroidism and is associated with chronic thyroiditis) on C cells is unclear in humans [5].

Branchial Cysts

Two patients with chronic lymphocytic thyroiditis with cystic nodules in the thyroids have been described [22]. These lesions resemble branchial cleft cysts in the lateral neck in that they are composed of lymphoid tissue with germinal centers and squamous lining in the cysts. The lining epithelium is bland and benign. These lesions occur in the lateral aspects of the thyroid lobes and have been considered cystic dilations of branchial remnants.

The association of many of these branchial-related lesions with autoimmune thyroid disease is intriguing [9, 19, 22, 25]. The immunological mechanisms that produce autoimmune thyroid disease by acting on thyroid follicular cells may affect branchial (thymic) epithelium and cause proliferation of these cells. Perhaps the

immunological abnormalities affect follicles derived from the ultimobranchial body similar to the follicles derived from the median thyroid anlage. It is unknown how many, if any, of the follicles in the lateral areas of the thyroid are derived from the ultimobranchial body, nor is the immunological makeup of these follicles known, if they exist. It is interesting to speculate what the interaction of these follicles, or at least the epithelium of the branchial remnants in the thyroid, may be in autoimmune thyroid disease. Perhaps this is an area worthy of investigation by immunopathologists and immunobiologists; it might shed light on the embryological associations between the lymphoid-rich branchial remnants and the thymic- and bone marrow-derived immune cells in adult patients with autoimmune thyroid dysfunction.

Whether all these lesions that have been postulated to arise from branchial or thymic rests in the thyroid, or both, are related remains speculative. The finding of apparently normal thymus in the thyroid [10, 25] in association with these lesions lends credence to this histogenetic theory. Conclusive proof awaits the discovery of markers (immunological, genetic, or both) specific for thymic or branchial epithelium. In the meantime, the grouping of these varied lesions as a spectrum of nonneoplastic, neoplastic, benign, and malignant lesions related via their embryology remains an attractive hypothesis.

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