Cystic Tumor of the Atrioventricular Node of the Heart Appears to Be the Heart Equivalent of the Solid Cell Nests (Ultimobranchial Rests) of the Thyroid

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Abstract

We studied a series of 10 solid cell nests (SCNs) of the thyroid and a case of cystic tumor of the atrioventricular node (CTAVN) of the heart and reviewed the literature. The CTAVN and SCNs appeared as cystic and/or solid (squamoid) structures mainly composed of polygonal or oval cells (main cells) admixed with occasional clear cells (neuroendocrine and C cells). Main cells were immunoreactive for simple and stratified epithelial-type cytokeratins, epithelial membrane antigen, carcinoembryonic antigen, carbohydrate antigen 19.9, p63, bcl-2, and galectin-3. Neuroendocrine (and C) cells were positive for simple-type cytokeratins, carcinoembryonic antigen, calcitonin, chromogranin, synaptophysin, and thyroid transcription factor-1.

Our data support the hypothesis that the CTAVN of the heart and the SCNs of the thyroid are identical structures that represent the same lesional process. The assumption that CTAVN is a ultimobranchial heterotopia fits with the known role of cardiac neural crest cells in cardiovascular development.

Solid cell nests (SCNs) are a normal component of the human thyroid gland.[1-8] They are thought to represent remnants of the ultimobranchial body, which in turn is derived from the branchial cleft pouch complexes IV and V. They are composed of solid (squamoid) and/or cystic structures of polygonal or oval cells (main cells) with occasional clear cells (C cells). Mixed follicles, glandular lumina, papillary structures, mucinous cells, and ciliated cells also are often present in the SCNs of the thyroid. Our group[1,3,9] and others[10] proposed that main cells of the SCNs represent a pool of stem cells of the normal adult thyroid.

The cystic tumor of the atrioventricular node (CTAVN) is a benign cystic mass located at the base of the atrial septum of the heart, in the region of the atrioventricular node.[11-21] Microscopically, the CTAVN is composed of solid and/or cystic structures of epithelial cells with a second population of neuroendocrine cells numerically less conspicuous.[16-18,22,23] It is a clinicopathologic entity that can occur as an incidental finding at autopsy or produce syncope or sudden death associated with complete heart block. It has been dubbed as the "smallest human tumor which causes sudden death,"[19] and almost all published cases were diagnosed at postmortem examination. More recently, 4 cases have been diagnosed antemortem and treated successfully with surgical excision.[11-13,20]

Divergent opinions about the histogenesis of CTAVN have resulted in numerous terms such as lymphangioendothelioma,[21] dysontogenetic endodermal tumor,[24] mesothelioma,[20] a remnant of the truncus arteriosus division (hamartoma),[25] hamartoma,[24] epithelial inclusion,[25] inclusion cyst,[26] endodermal inclusion,[24] chronic lymphangitis proliferans,[25] adenoma-like tissue malformation of the serosal epithelium,[25] heterotopic

epithelial replacement of the atrioventricular node,[27] congenital polycystic tumor,[28] congenital endodermal heterotopia,[29] polycystic tumor of the atrioventricular node,[22] and simply tumor of the atrioventricular nodal region.[30]

The morphologic resemblance between CTAVN and SCNs led us to hypothesize that they might represent the same lesion. To evaluate this possibility, we studied the clinical, morphologic, histochemical, and immunohistochemical features of a series of 10 SCNs and a case of CTAVN and put our data together with those obtained in a thorough review of the literature.

Materials and Methods

Cases

We obtained 10 cases featuring SCNs of the thyroid gland and 1 case of CTAVN by reviewing the microscopic slides of files of the Department of Pathology, Clinical University Hospital, Santiago de Compostela, Spain. Formalin-fixed, paraffin wax–embedded tissue samples were obtained from 10 cases of SCNs (patients were 8 women and 2 men; age range, 31-68 years) and from the autopsy of a 75-year-old man with a previously reported CTAVN.[18] The pathologic findings in the 10 surgical thyroid specimens were multinodular goiter in 5 cases, follicular adenoma in 2 cases, multinodular goiter and follicular adenoma in 2 cases, and multinodular goiter and lymphocytic thyroiditis in 1 case. The patient with CTAVN had cardiac failure, and electrocardiography revealed first-degree atrioventricular block and left bundle branch block. He died immediately after admission, and the autopsy findings indicated cardiogenic shock as the cause of death.

Histologic, Histochemical, and Immunohistochemical Analysis

In every case, 4-μm serial histologic sections were cut, mounted in silane-coated slides, and stained with H&E, alcian blue (pH 2.5), alcian blue–periodic acid–Schiff, and Mayer mucicarmine. Immunohistochemical analysis on paraffin-embedded material was performed using a universal second antibody kit that used a peroxidase-conjugated labeled-dextran polymer (EnVision, Peroxidase/DAB; DAKO, Glostrup, Denmark).

A commercially available panel of monoclonal and polyclonal antibodies was used for the following: epithelial markers: cytokeratin (CK) 7 (clone OV-TL 12/30, dilution 1:50, antigen retrieval water bath and Proteinase K, DAKO), CK8 and CK18 (CAM5.2, prediluted, water bath and Proteinase K, Becton Dickinson, Mountain View, CA), CK1 through CK8, CK10, CK13, CK14, CK16, and CK19 (AE1-AE3, dilution 1:20, water bath and Proteinase K, DAKO), CK1, CK5, CK10, and CK14 (34βE12, dilution 1:10, water bath and Proteinase K, Enzo, Farmingdale, NY), CK20 (Ks 20.8, dilution 1:20, water bath and Proteinase K, DAKO), and epithelial membrane antigen (EMA; E29, dilution 1:50, microwave oven, DAKO); thyroid markers: thyroid transcription factor-1 (8G7G3/1, dilution 1:50, water bath, DAKO), thyroglobulin (Tg6, dilution 1:2,000, DAKO), and calcitonin (polyclonal, dilution 1:1,000, BioGenex, San Ramon, CA); neuroendocrine markers: chromogranin A (LK2H10, dilution 1:100, water bath and EDTA, BioGenex) and synaptophysin (SY38, dilution 1:100, microwave oven, BioGenex); markers of SCNs: carcinoembryonic antigen (CEA; polyclonal, dilution 1:4,000, DAKO), p63 (4A4, dilution 1:50, water bath, DAKO), galectin-3 (9C4, dilution 1:200, Novocastra, Newcastle upon Tyne, England), and bcl-2 (124, dilution 1:10, DAKO); vimentin (V9, dilution 1:5,000, microwave oven, BioGenex); markers of endothelial differentiation: CD31 (JC70A, dilution 1:10, microwave oven, DAKO) and factor VIII–related antigen (F8/86, dilution 1:40, microwave oven, DAKO); calretinin as a marker of mesothelial differentiation (Dak-Calret 1, dilution 1:50, microwave oven, DAKO); carbohydrate antigen 19.9, a carbohydrate antigen related to the Lewis A blood group antigen (c241:5:1:4, dilution 1:400, microwave oven, Novocastra); and hormone receptors: estrogen receptor (6F11, dilution 1:10, microwave oven, Novocastra) and progesterone receptor (PgR 636, dilution 1:50, water bath, DAKO). Diaminobenzidine was used as a chromogen.

Negative control samples (the primary antibody was replaced by nonimmune mouse serum) and positive control samples were included in each slide run. For p63, thyroid transcription factor-1, and estrogen and progesterone receptors, only nuclear immunoreactivity was considered specific positivity. For EMA, only a membranous pattern was considered positive. For all other markers, only cytoplasmic staining was accepted as indicating immunoreactivity.

Results

Among the 10 cases of SCNs, 2 cases displayed only solid cell structures, and 8 cases displayed mixed solid nests and microcystic structures. In the CTAVN, we observed solid cell nests and microcystic cavities. The CTAVN and SCNs were composed of 2 distinctive cell types: (1) main cells, which are polygonal to elongated or even spindle-shaped cells with centrally located, oval nuclei with frequent grooves and deeply eosinophilic cytoplasm with squamoid features but lacking intercellular bridges; and (2) a minor proportion of cells characterized by clear cytoplasm and centrally located, small compact nuclei **Image 1** and **Image 2**. Mixed follicles, partially

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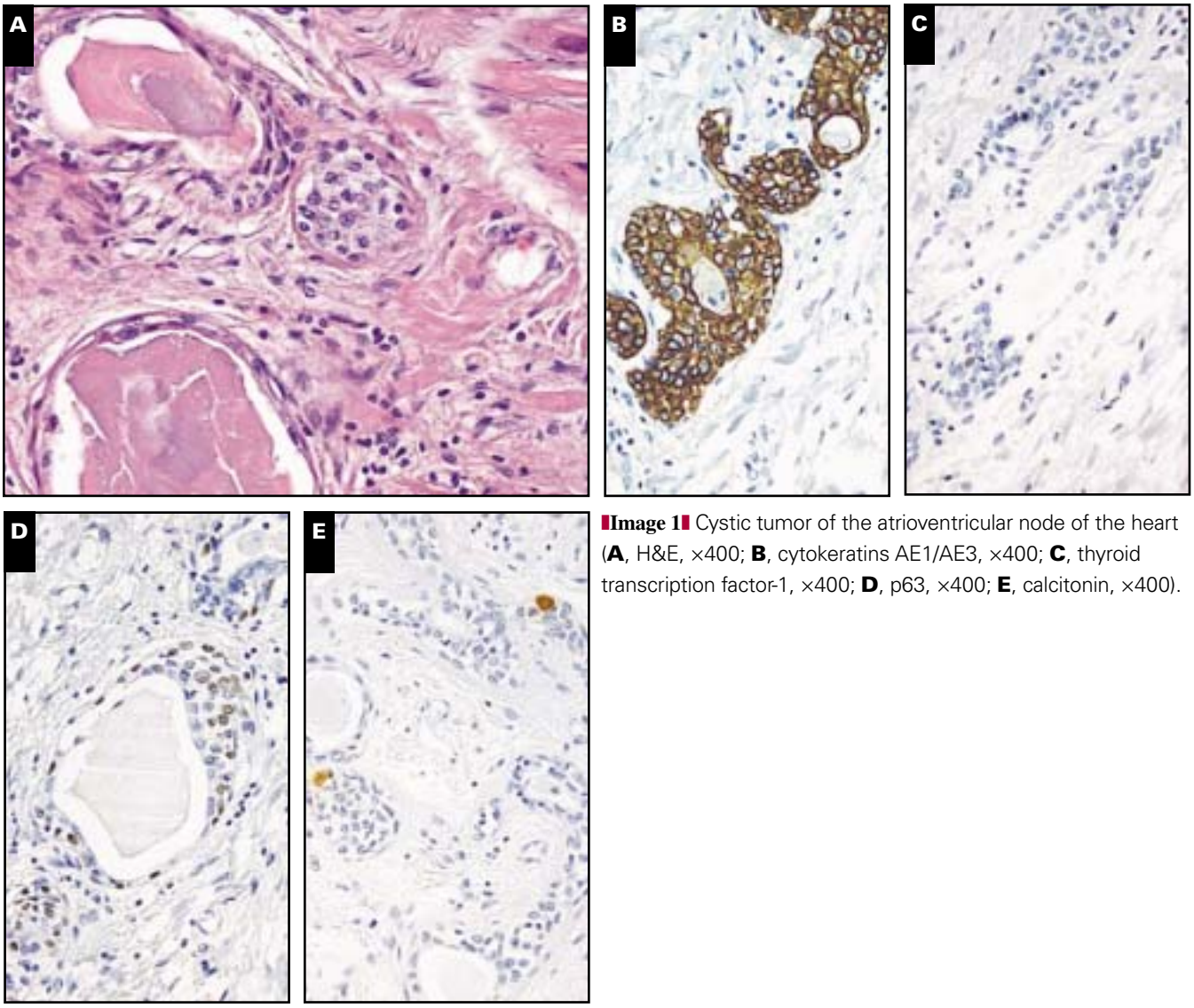

Image 1 Cystic tumor of the atrioventricular node of the heart (**A**, H&E, ×400; **B**, cytokeratins AE1/AE3, ×400; **C**, thyroid transcription factor-1, ×400; **D**, p63, ×400; **E**, calcitonin, ×400).

composed of main cells and partially depicting cuboidal cells with eosinophilic cytoplasm and round to oval nuclei, were found in 4 cases of SCNs. Ciliated cells were observed in the lining of microcysts associated with CTAVN and in 1 case of SCNs and in cases reported in the literature.[1,31] Mucosubstances also were found in CTAVN and SCNs as previously reported.[5-8,16,23,29,32]

The immunohistochemical study of the CTAVN and SCNs provided similar, almost identical results, as shown in **Table 1**. Main cells in the CTAVN and SCNs expressed positivity for cytokeratins (CAM5.2, AE1/AE3, 34βE12, and CK7), EMA, CEA, carbohydrate antigen 19.9, p63, bcl-2, and galectin-3 (Images 1 and 2). In all cases, a second cell population of isolated cells was positive for cytokeratins (CAM5.2 and AE1/AE3), EMA, CEA, calcitonin, chromogranin, synaptophysin, and thyroid transcription factor-1 (Images 1 and 2). All cases were consistently negative for CK20, thyroglobulin, vimentin, CD31, factor VIII–related antigen, calretinin, estrogen receptor, and progesterone receptor.

Discussion

Our findings, together with data from the literature, suggest that the CTAVN and the SCNs of the thyroid are similar structures. Both entities basically are composed of solid and/or cystic nests of squamoid cells (main cells) with a minor population of neuroendocrine cells (C cells). The latter cells contain argyrophil granules but not argentaffin granules.[22,28] The ultrastructural study of CTAVN[16,29,30,35] and SCNs[36] show main cells characterized by cytoplasmic tonofilaments and desmosome-like structures and neuroendocrine or C cells with electron-dense secretory granules.

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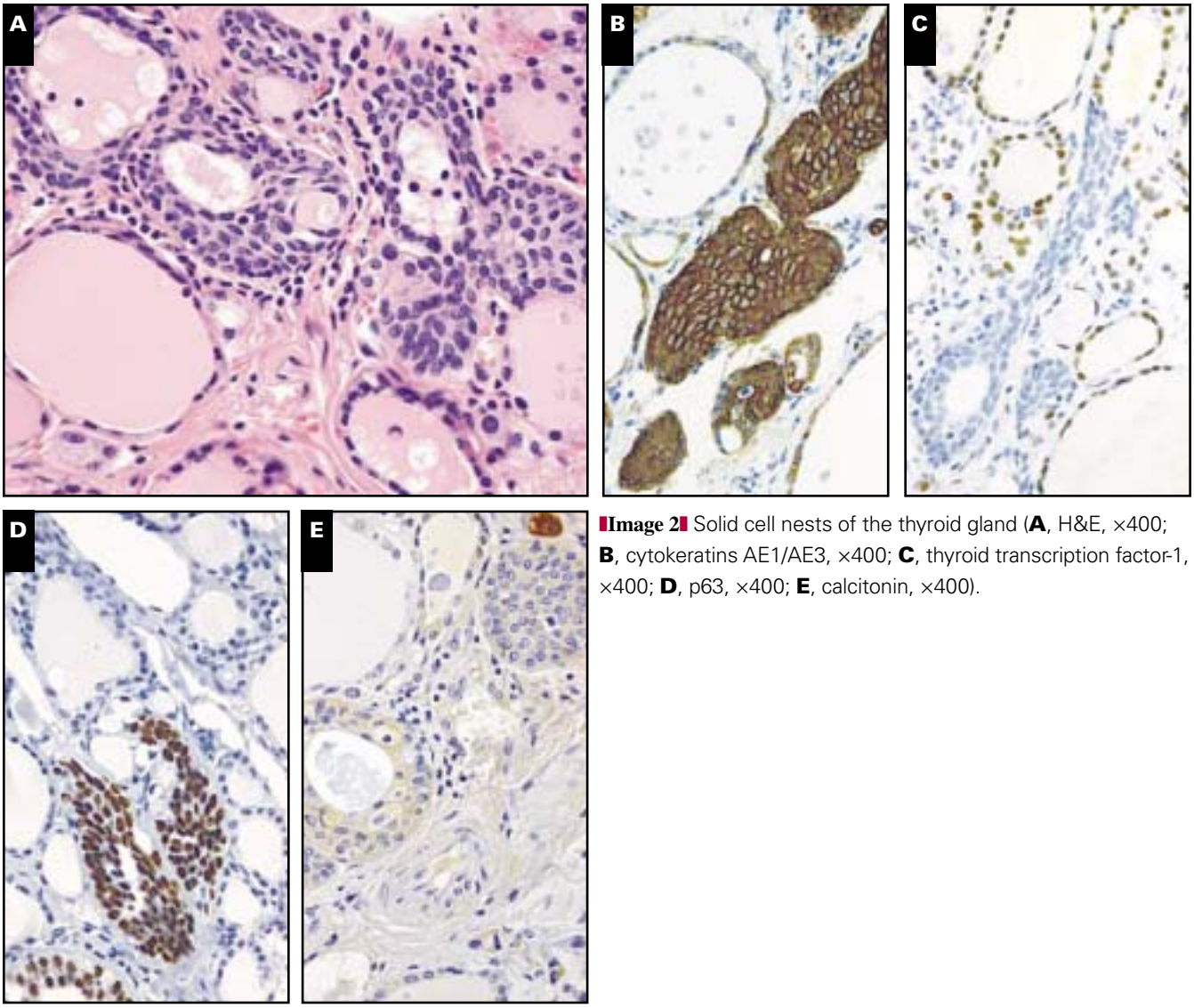

Image 2 Solid cell nests of the thyroid gland (**A**, H&E, ×400; **B**, cytokeratins AE1/AE3, ×400; **C**, thyroid transcription factor-1, ×400; **D**, p63, ×400; **E**, calcitonin, ×400).

In the human thyroid gland, C cells proceeding from the neural crest migrate to the ultimobranchial bodies during development and subsequently are incorporated into the lateral lobes of the thyroid. The topographic distribution of the SCNs in the thyroid gland, their association with C cells and with different tissues related to branchial structures,[1,4,37] and the presence of SCNs in some piriform sinus fistulas (as remnants of the ultimobranchial body)[38] have been proposed as evidence of the ultimobranchial origin of SCNs. Marked similarities have been pointed out between SCNs and the ultimobranchial body of the rat[39] and wild mammals.[40]

The discovery in the chick embryo that a specific region of the neural crest, termed the *cardiac neural crest,* is essential for septation of the cardiac outflow tract and for aortic arch artery development, has led to the classification of a series of human cardiac defects as neural crest–associated.[41] We think that alterations in the development of the cardiac neural crest could explain the presence of ultimobranchial rests in the atrioventricular node region, known as CTAVN, which are identical to the SCNs of the thyroid.

Disorganized neural structures have been described in the atrioventricular node region[42] and also have been associated with the SCNs.[1] An angiomatous variant of the CTAVN was reported.[43] Teratomatous elements also have been reported as closely connected with SCNs, indicating that the main cells might serve as multipotential stem cells.[1] The description of teratomas in the atrioventricular node region[44] fits with our hypothesis that SCNs and CTAVN are identical lesions. Mixed follicles are structures lined by main cells and follicular cells that are present characteristically in SCNs.[1,3,4,6] It has been proposed that mixed follicles of SCNs represent differentiation toward follicular cells of the thyroid through a process of maturation of the main

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Table 1
Immunohistochemical Findings

	CTAVN		SCNs	
Antibody	**Main Cells**	**Neuroendocrine Cells**	**Main Cells**	**C Cells**
CK-CAM5.2[3,13,17,23*]	+	+	+	+
CK-AE1/AE3[3,15,23*]	+	+	+	+
CK-34βE12[3,7,8*]	+	–	+	–
CK7[3*]	+	–	+	–
CK20[3*]	–	–	–	+/–
EMA[12,15,16,22,23,28,32,33*]	+	+	+	+
TTF-1[3*]	–	+	–	+
Thyroglobulin[3,4,6,7,13,17,22,23*]	–	–	–	–
Calcitonin[2-4,6-8,17,23,28,32,36*]	–	+	–	+
Chromogranin[4,6,16,17,22,23*]	–	+	–	+
Synaptophysin[*]	–	+	–	+
CEA[2,3,6-8,11,13-17,22,23,29,30,32,34*]	+	+	+	+
p63 protein[1,3,10*]	+	–	+	–
Galectin-3[2*]	+	–	+	–
bcl-2[1*]	+	+	+	+
Vimentin[6,14,23,32*]	–	–	–	–
CD31[23*]	–	–	–	–
Factor VIII[13,14,17,22,23,28,32,34*]	–	–	–	–
Calretinin[*]	–	–	–	–
CA 19.9[16*]	+	+/–	+	+/–
Estrogen receptor[*]	–	–	–	–
Progesterone receptor[*]	–	–	–	–

CA 19.9, carbohydrate antigen 19.9; CEA, carcinoembryonic antigen; CK, cytokeratin; CTAVN, cystic tumor of the atrioventricular node; EMA, epithelial membrane antigen; SCNs, solid cell nests; TTF-1, thyroid transcription factor-1; +, positive; –, negative; +/–, equivocal results.
[*] Present series.

cells.[1,3,6] This might explain the cases of intracardiac thyroid tissue[45] and cases of coexistence of ectopic thyroid and CTAVN in the heart.[46]

Congenital CTAVN can occur in patients with complex congenital heart disease,[47] thyroglossal duct cysts,[47] coexisting cysts in the ovaries and breast,[48] polycystic ovaries,[34] ventricular septal defect,[30] nasal septal defect,[47] Dandy-Walker anomaly,[30] encephalocele,[47] thinning of the corpus callosum,[47] absent septum pellucidum,[47] Meckel diverticulum,[30] hyperplasia of the islets of Langerhans, thymic hyperplasia, adrenal tissue heterotopia, clear cell adenomatosis in the kidney,[17] and/or Emery-Dreifuss muscular dystrophy.[22] Possible familial occurrence,[35] association with midline defects, and association with other congenital lesions suggest a genetic defect involving migration of embryologic tissues in patients with CTAVN.[47]

CTAVN also has been reported in rats.[49] Several mammalian models of outflow defects have been described, and there is an increasing list of gene mutations associated with different combinations of neural crest–related defects.[41] The study of these mammalian models might contribute to clarify the molecular bases involved in these defects of neural crest derivatives.

Based on the present data and a review of the literature, similarities between the CTAVN of the heart and SCNs of the thyroid indicate that they are basically identical lesions. The CTAVN represents an ultimobranchial heterotopia, and its histogenesis is congruent with an alteration in cardiac neural crest cell development.

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Dedicated to the memory of Professor Sergio Vidal.

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