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Solid cell nests of the thyroid gland

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Summary. The histogenesis and clinical significance of solid cell nests (SCN) of the thyroid are not fully understood. From August 1987 to December 1989 a total of 2544 patients with thyroid and parathyroid diseases underwent surgery at Ito Hospital, and SCN were revealed within the thyroid parenchyma in 21 (0.8%). Distribution of SCN was not limited to the upper one-third of the lateral lobe, and SCN were found even in the isthmus lobe. In 5 cases microcysts were also noted within SCN, and their content was thought to be acidic proteoglycan. Immunohistochemical study revealed that SCN were negative for thyroglobulin and calcitonin but positive for carcinoembryonic antigen. Thirteen of 21 cases showed positive immunostaining with cytokeratin. Scattered calcitonin-positive cells were noted around the SCN. It is suggested from these findings that SCN of the thyroid are closely related to certain cells of ultimobranchial body vestiges which may be not of neuroectodermal origin but of endodermal origin.

Key words: Solid cell nests – Thyroid gland

Introduction

On some occasions, aggregation of epidermoid cells, so-called solid cell nests (SCN), can be seen in the histological specimens of thyroid glands. In 1907 Getzowa described these structures and considered them to be of ultimobranchial body origin. Since then, Jaffé (1937), Yamaoka (1973), Kakudo et al. (1977), Janzer et al. (1979), Harach (1985a–c, 1988) and Autelitano et al. (1987) have studied SCN and have suggested that these cells might be squamous cells, or might represent C-cell hyperplasia, an early stage of medullary thyroid carcinoma or mucoepidermoid carcinoma.

These reports were based mainly upon studies of autopsy cases, and only a few papers have reported clinical studies of patients with thyroid disorders. We studied SCN of the thyroid gland found by routine pathological examination of surgical specimens of patients with diseases of the thyroid and parathyroid glands in order to establish the incidence of SCN in these materials and also to speculate on the origin of SCN.

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Materials and methods

The numbers of patients with thyroid and parathyroid disorders were 2518 and 26, respectively, who underwent surgery at Ito Hospital from August 1987 to December 1989. Surgical specimens were routinely fixed with formalin, embedded in paraffin, sections were stained with haematoxylin and eosin (H & E) and used for routine pathological diagnosis (3.3 sections per case on average). In 21 cases, SCN were found within the normal thyroid parenchyma adjacent to the nodules of the thyroid gland as well as to the parathyroid adenomas. (In parathyroid adenoma cases adjacent normal thyroid tissue was also resected in this series.) There were 5 males and 16 females, and age at surgery ranged from 37–69 years (mean ± SD: 52 ± 8 years). The number of cases with SCN and the incidence in each lesion are listed in Table 1. The overall incidence of SCN was 0.8%.

Table 1. Incidence of solid cell nests (SCN) for each lesion of the thyroid and parathyroid glands (August 1987 – December 1989)

Lesion	Total number of surgical cases	Number of cases with SCN	%
Thyroid:			
Carcinoma	661	13	2.0
Adenoma	358	4	1.1
Adenomatous goitre	646	2	0.3
Graves' disease	854	1[a]	0.1
Parathyroid:			
Adenoma	26	2	7.7
Total	2544	21	0.8

[a] This case also involved adenoma

Serial sections were obtained from the paraffin blocks in which SCN were noted in H & E section, and were used in the histochemical and immunohistochemical studies. Neutral polysaccharide and acidic proteoglycan were studied by periodic acid-Schiff (PAS)-alcian blue staining. Thyroglobulin, calcitonin, carcinoembryonic antigen (CEA), cytokeratin, vimentin, and epidermal growth factor (EGF) were studied immunohistochemically using the avidin-biotin peroxidase complex (ABC) method (Hsu et al. 1981). Serial sections were cut 2 μm thick, deparaffinized and endogenous peroxidase activity was blocked by adding 0.3% methanolic hydrogen peroxide followed by normal goat serum. Primary antibody (rabbit anti-human IgG) was added and incubated at 37° C. Biotin-labelled goat anti-mouse IgG was then added as the second antibody, followed by ABC and diaminobenzidine tetrahydrochloride. Counterstaining was performed with haematoxylin. As the second antibodies, polyclonal anti-thyroglobulin antibody (Dakopatts Glostrup, Denmark), polyclonal anti-calcitonin and anti-CEA antibodies (BioGenex San Ramon, Ca, USA), monoclonal anti-cytokeratin and anti-vimentin antibodies (BioGenex), and polyclonal anti-EGF antibody (Wakunaga Osaka, Japan) were used.

Serum thyroglobulin, calcitonin and CEA were measured by radioimmunoassay.

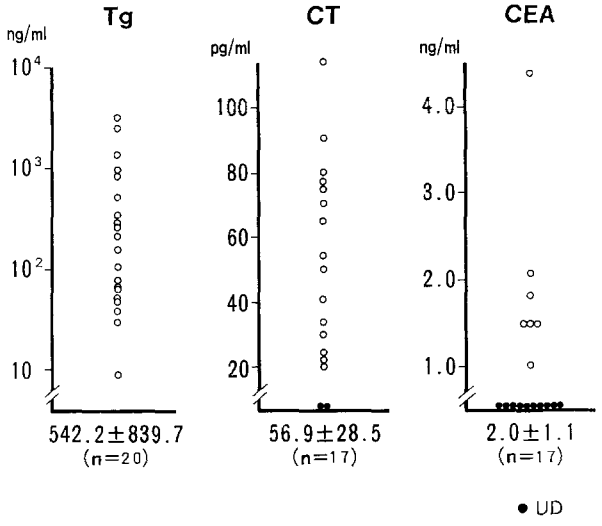

Fig. 1. Serum thyroglobulin (*Tg*), calcitonin (*CT*) and carcinoembryonic antigen (*CEA*) in patients with solid cell nests (SCN) of the thyroid at admission. Numerals at the bottom indicate mean ± SD. *n* Number of cases tested; *UD*, undetectable

Results

Clinical findings

Thyroid nodules of any kind were located within the right lobe in 9 cases, left lobe in 5, both lobes in 4, and within the isthmus in 1; on the other hand, they occupied the whole gland in 4 cases, upper pole of the lobe in 1, centre of the lateral lobe in 9, lower one-third of the lobe in 3, lower pole of the lobe in 1, and the isthmus in 1. Serum calcitonin levels at admission in these cases ($n=17$) were all normal, ranging from less than 10.0–115.2 pg/ml, and serum CEA levels ($n=17$) were also normal except in 1 case, where it was 4.4 ng/ml. Serum thyroglobulin ($n=20$) ranged from 9.0–3051 ng/ml. No case was positive for anti-thyroglobulin antibody (Fig. 1).

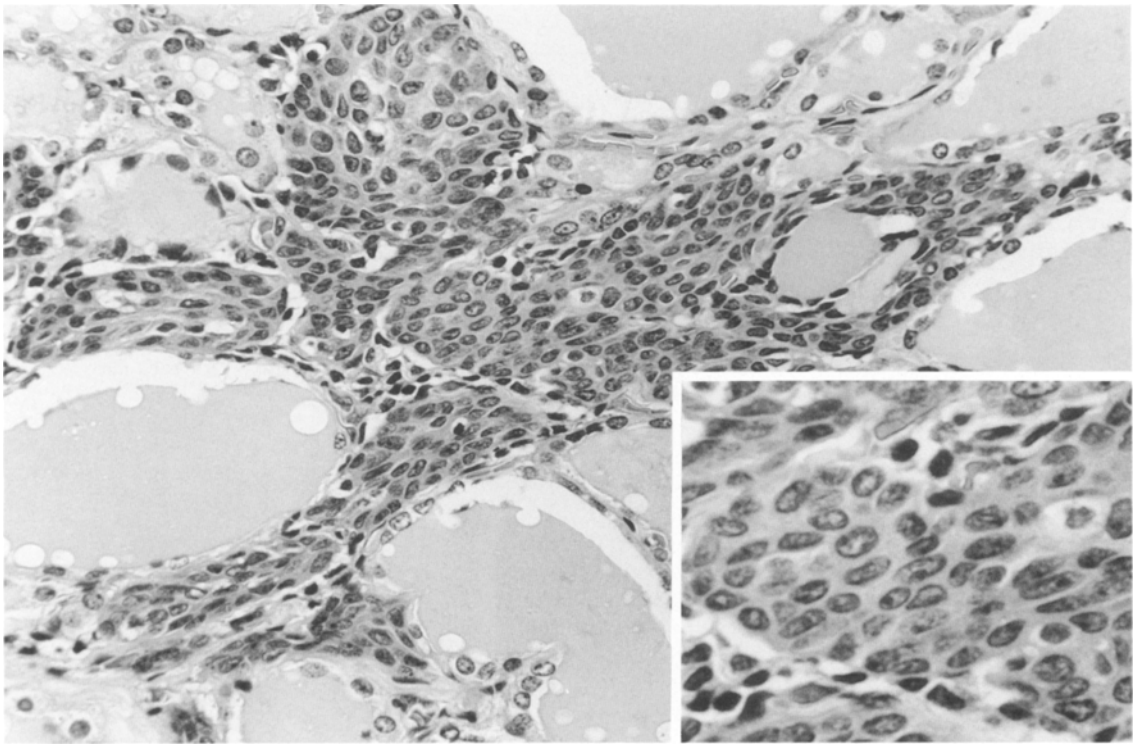

Fig. 2. Histological findings of SCN of the thyroid. SCN were located outside the basal lamina of and in between the thyroid follicles. Proliferation of SCN into the follicular lumina was not observed. H & E, ×400. *Inset*: Cells were spindle-shaped or pleomorphic and contained oval, spindle-shaped or polymorphic large nuclei. H & E, ×800

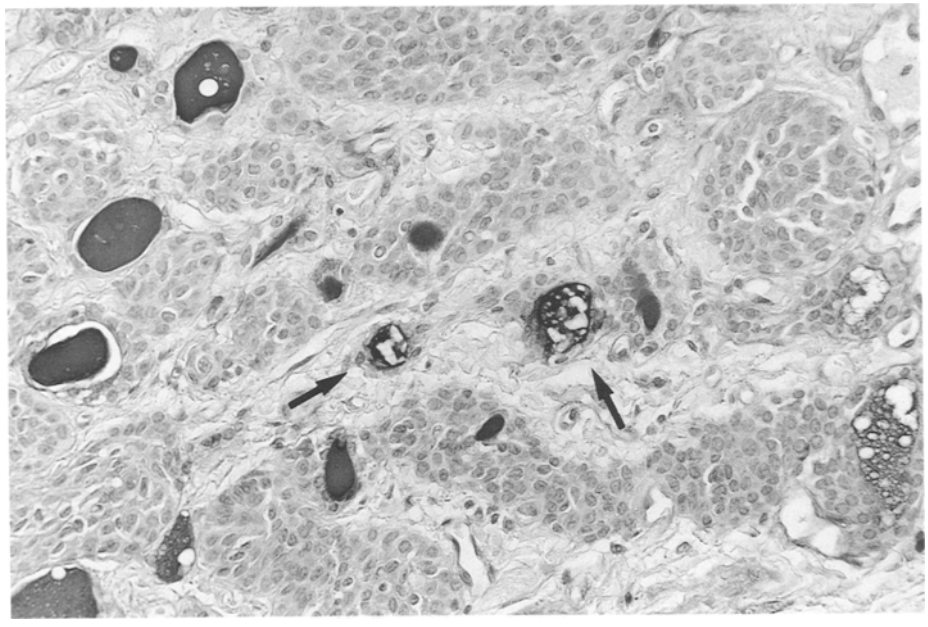

Fig. 3. Microcyst-like structure in SCN. Contents were alcian blue positive. Periodic acid-Schiff (PAS)-alcian blue, ×400

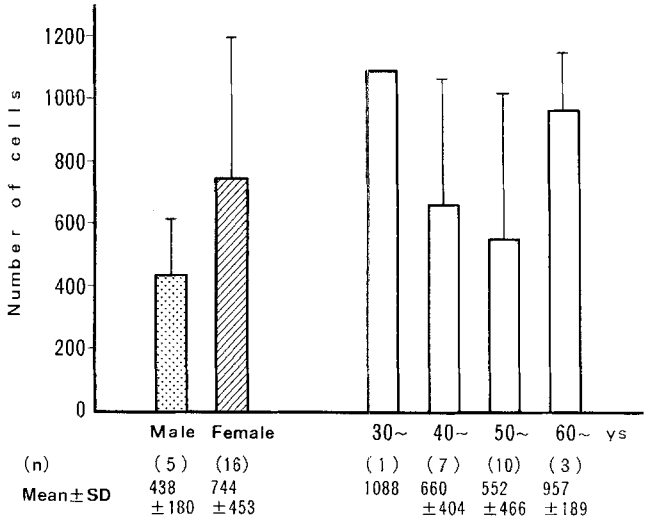

Fig. 4. Number of cells in SCN of the thyroid according to sex and age group. Overall number of cells was 671 ± 422 (mean ± SD). *n*, Number of cases

Histological and histochemical findings

SCN were located outside the basal lamina of and in between the thyroid follicles, and the proliferation of SCN was not observed between the follicular cells or into the follicular lumina (Fig. 2).

The cells which constitute SCN were larger than follicular epithelial cells, were spindle-shaped or polygonal, and contained oval, spindle-shaped or polymorphic and basophilic large nuclei. The nuclear membrane was thick, chromatin was coarse, and one or two nucleoli were large and prominent. It showed variations in the N/C ratio, and lucid areas and vacuoles were occasionally seen around the nuclei within the cytoplasms. Neither intercellular bridges, cornifications nor concentric pearl formation was observed (Fig. 2, inset).

Within SCN a microcyst-like structure was found in 5 cases, which differed from thyroid follicles. The content of this cystic structure differed from the colloid of thyroid follicles in that it was thyroglobulin negative and alcian blue positive, this being indicative of acidic proteoglycan (Fig. 3).

The number of cells of SCN was 671 ± 422 (mean ± SD), ranging from 150–1810. No statistical differences were noted between males and females and between the age groups (Fig. 4).

Immunohistochemical findings

SCN showed negative immunostaining with anti-thyroglobulin antibody in all cases, and immunostaining for calcitonin was also negative in all cases except for 1 case each of papillary carcinoma, adenomatous goitre, and parathyroid adenoma. In contrast, immunoreactivity for CEA was positive in all cases, 10 cases being strongly positive (Fig. 5). While most of the SCN themselves showed negative immunostaining with anti-calcitonin antibody, many calcitonin-positive cells were revealed scattered around the SCN, but in 9 cases these cells were negative for CEA. Immunoreactivity of SCN for cytokeratin was positive in 13 cases, whereas 12 cases were negative for vimentin. Twelve cases showed positive immunostaining for EGF, but 4 cases showed negative reactivity.

Discussion

In 1907 Getzowa first described SCN within the thyroid parenchyma, considering them to be of ultimobranchial body origin. Later, Jaffé (1937) suggested that these cells originated from thyroid epithelial cells which were transformed through squamous metaplasia. Fukunaga and

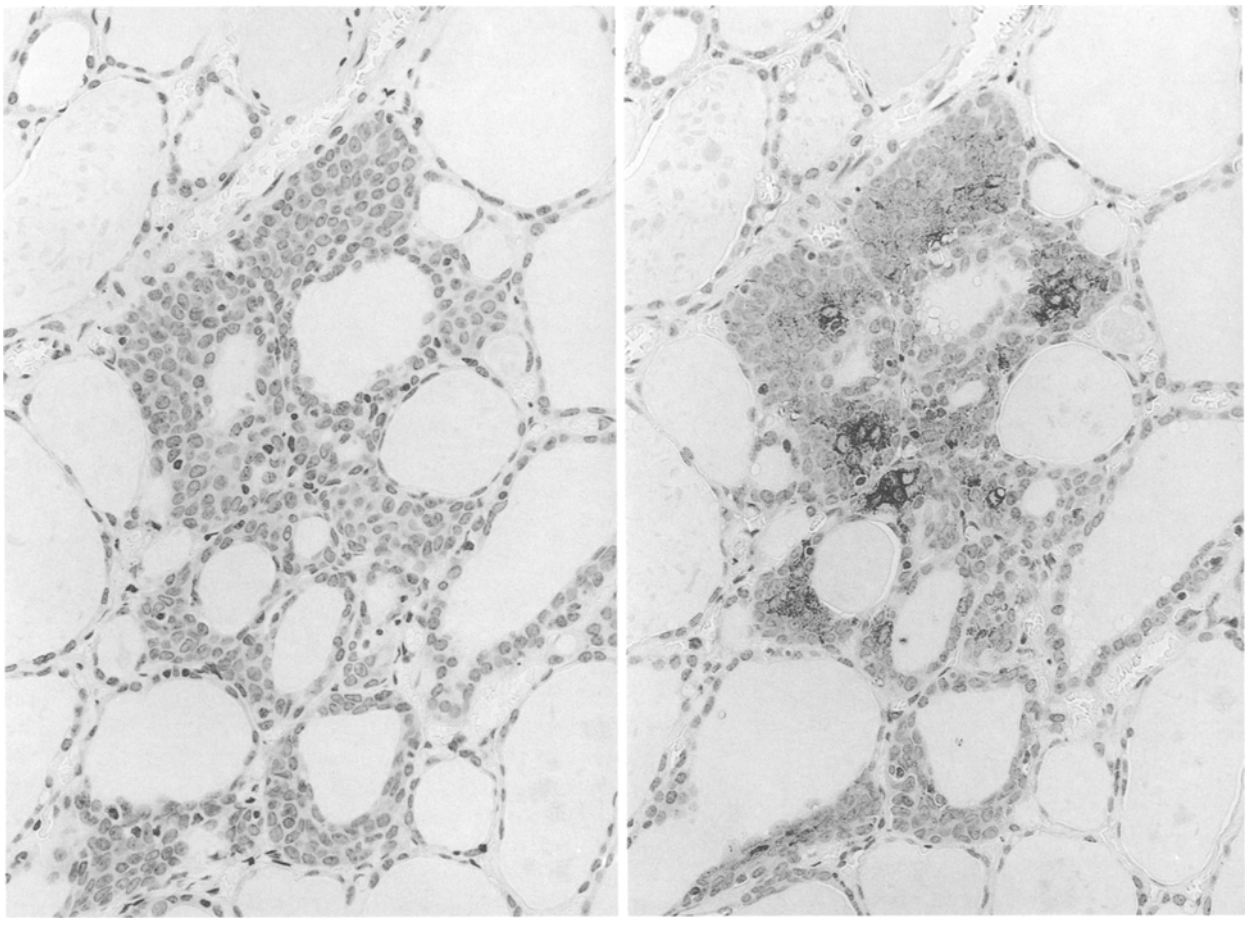

Fig. 5. Immunohistochemical findings of SCN of the thyroid. Cells are seen to be calcitonin negative (*left*) but CEA positive (*right*), ABC method, ×400

Lockett (1971) and Autelitano et al. (1987), however, indicated that SCN were latent medullary thyroid carcinomas. Yamaoka (1973), on the other hand, concluded that SCN were neither latent medullary thyroid carcinoma nor metaplastic follicular cells. More recently, Nadig et al. (1978) and Janzer et al. (1979) described SCN as vestiges of the ultimobranchial body. In contrast, Harach (1985a) suggested the existence of a relationship between SCN and mucoepidermoid carcinoma. As reviewed above, the histogenesis of SCN can be summarized as follows: (1) ultimobranchial body – C-cells, (2) squamous metaplasia of follicular epithelial cells, and (3) epidermoid cells.

The incidence of SCN reported in the literature varies from 7% (Janzer et al. 1979) to 60% (Harach 1985b). This difference seems to be related to the methods of investigation of specimens; the incidence rises as the number of sections increases (Harach 1988). These investigations of SCN were based mainly on autopsy cases studied by serial sections of specimens, and only a few studies have looked at SCN incidence in relation to thyroid disease (Vollenweider and Hedinger 1988). In our present study surgically resected thyroid tissues were used as materials, and routine examination for pathological diagnosis was carried out. This may be the main reason why the incidence of SCN was lower in our series compared to those in other reports.

Distribution of SCN in the thyroid tissue was reported to be maximal in the upper one-third of the lateral lobe, and SCN has not been found previously in the isthmus lobe (Yamaoka 1973; Janzer et al. 1979; Harach 1985b). Moreover, immunohistochemical study revealed that SCN showed positive immunostaining for calcitonin (Autelitano et al. 1987). These findings suggest that SCN may be related embryologically to the ultimobranchial body vestiges and C-cells. In contrast, however, our present study revealed that SCN were found even in the isthmus lobe, and that most of them were immunohistochemically negative for calcitonin. These findings may suggest that SCN are not closely related to C-cells. This suggestion can be supported by the fact that the localization of SCN in the thyroid parenchyma and their mode of proliferation are quite different from that in C-cell hyperplasia, as described by DeLellis and Wolfe (1981) and Wolfe and DeLellis (1981). Calcitonin-positive cells, on the other hand, were found scattered around the SCN, which also suggests that SCN may be related embryologically to ultimobranchial body vestiges other than C-cells.

The relationship of SCN to epidermoid-squamous cells would be a pertinent issue if SCN and C-cells were not closely related. The opinion has been expressed that SCN are transformed from the follicular epithelial cells through squamous metaplasia (Jaffé 1937; Kakudo et al.

1977). However, it is difficult to consider that a particular cell group would undergo squamous metaplasia spontaneously without any changes of foregoing inflammation or dystrophy. Vollenweider and Hedinger (1988) reported that epidermoid cell nests within the thyroid tissue in Hashimoto's disease were SCN themselves and not metaplastic follicular cells. The fact that continuous or obvious transformation of follicular cells into SCN is not observed is also a finding against squamous transformation of follicular cells.

Harach (1985a, c) found that within SCN there was a second kind of cell which contained alcian-blue-positive materials and that author considered these cells to be epidermoid cells showing mucinous degeneration. He also suggested that mucoepidermoid carcinoma of the thyroid originated either from SCN or from ultimobranchial body vestiges because immunostaining for epidermal keratin was positive in SCN as well as in mucoepidermoid carcinoma. Katoh et al. (1990) also indicated similarity of mucoepidermoid carcinoma and SCN of the thyroid. In our present study a microcyst-like structure was noted within SCN in 5 of 21 cases and the contents of these microcysts were alcian blue positive. The finding that many cases showed positive immunoreactivity for cytokeratin strongly suggests a close relationship between SCN and epidermoid cells of the thyroid. It seems worth noting that SCN were negative for calcitonin but positive for CEA. Harach (1985b) further suggested the possibility that ultimobranchial body vestiges, which he regarded as the origin of SCN, were not of neuroectodermal origin but of endodermal origin. Recently, much attention has been given to such evidence of mucus-producing medullary thyroid carcinoma (Fernandes et al. 1982) or thyroid carcinoma composed of both follicular and parafollicular cells (Ljungberg et al. 1983; Ogawa et al. 1989), and it is indicated that some of these cells, formerly regarded as cells of the APUD system, might be of endodermal origin. SCN of the thyroid may represent cell structure of endodermal origin of ultimobranchial body vestiges, different from C-cell components.

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