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Thyroid Tubercle of Zuckerkandl May Not Arise from the Ultimobranchial Body: Results from Histological Analysis

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Keywords
Tubercle of Zuckerkandl · Ultimobranchial body · Anatomy · C cell · Solid cell nests

Abstract
Thyroid tubercle of Zuckerkandl (TZ) is a nodule arising from the posterolateral thyroid, considered to be a remnant of the ultimobranchial body (UB). Considering that C cells and solid cell nests also arise from the UB, we hypothesized that these would be present in the TZ. We examined the presence of C cells and solid cell nests in the TZ using the histological analyses of 21 patients with grade 2 or 3 TZs following Pelizzo's grading system. Out of 21 TZs, 19 (90.5%) were located in the right lobe of the thyroid. Microscopically, solid cell nests were found within the TZ in 1 case (4.8%), and within the main thyroid tissues in 3 cases (14.3%). Calcitonin-positive C cells were scattered within the TZ in 1 case (4.8%), and within the main thyroid tissue in 15 cases (71.4%). The distribution of C cells within the main thyroid tissue was denser than that within the TZ. The above-mentioned results indicated the lack of C cells and solid cell nests in the TZ. Although the TZ may have an embryological origin different from that of ordinary thyroid tissue, it is unlikely that the remnants of the UB are involved in the formation of the TZ.

Introduction

Thyroid tubercle of Zuckerkandl (TZ) is a protuberance or nodule arising from the posterolateral thyroid tissue [1–8]. It was first described in 1902 by the Viennese anatomist Emil Zuckerkandl as "Processus posterior glandulae thyroideae" [9]. The TZ is present in 60–83% of the patients undergoing thyroidectomy [1, 2, 5, 8, 10–13] and is mostly located in the mid-third of the thyroid lobe [1]. It is an important landmark for the identification of the recurrent laryngeal nerve during thyroid surgery because most recurrent laryngeal nerves pass beneath the TZ [1, 2, 5, 14].

Embryologically, the TZ has been described to correspond to the lateral anlagen [5, 8, 11, 15–18]. Thyroid tissue develops after the fusion of the median and lateral anlagen [19, 20]. The former descends from the foramen caecum and forms the main part of the thyroid tissue by the end of the third week of gestation [19]. The paired smaller lateral anlagen arise from the ultimobranchial body (UB) and attach to the posterior surface of the thyroid during the fifth week [19, 20]. The remnants of the UB, when present, are thought to persist as the TZ [5, 11, 13, 15].

It is well known that calcitonin-producing C cells and solid cell nests arise from the UB [19, 20]. To our knowl-

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edge, however, no study has elucidated whether C cells and solid cell nests are present in the TZ. Considering that they arise from the same anlagen, we hypothesized that the TZ would contain C cells and solid cell nests. Thus, the purpose of the present study was to examine the presence of C cells and solid cell nests in the TZ.

Materials and Methods

We identified 21 patients (2.9%) with the TZ from 787 thyroid tissue samples (total thyroidectomy, 259 cases; right lobectomy, 246 cases; and left lobectomy, 222 cases) resected at Kuma Hospital between July 2018 and June 2019. We defined the TZ as a gross lateral projection distinguishable from the lateral lobe of the thyroid. TZs were identified from formalin-fixed samples. Recognizable TZs of grade 2 or 3 according to Pelizzo's grading system [4] were included in this study (Fig. 1). Samples from patients with Graves' disease and Hashimoto's thyroiditis that showed lobulation and those with carcinoma near the TZ were excluded.

We observed histological preparations of the TZ and main thyroid tissue in hematoxylin and eosin-stained sections microscopically. Solid cell nests were defined as small (<1 mm) interfollicular clusters of epithelial cells resembling squamous/transitional epithelium. C cells were identified as calcitonin-positive cells using an anti-calcitonin primary antibody (Polyclonal, PA0406; Leica Biosystems, Newcastle, UK) and were visualized using the IgG-HRP linker and 3,3′-diaminobenzidine tetrahydrochloride hydrate chromogenic substrate. Immunohistochemical staining was performed using the automated Leica Bond-Max system and Bond Refine Detection Kit (Leica Microsystems, Wetzlar, Germany), according to the manufacturer's recommendations.

Results

Out of 21 samples, 11 (right: 10, left: 1) and 10 (right: 9, left: 1) were from total thyroidectomies and lobectomies, respectively. Among these, 1, 18, and 2 were located in the upper, middle, and lower third, respectively. The maximum dimension of TZs ranged from 5 to 15 mm (median 10.0). The main histological diagnoses of the resected thyroid tissue were as follows: papillary carcinoma (15), follicular carcinoma (2), follicular tumor of uncertain malignant potential (1), well-differentiated thyroid tumor of uncertain malignant potential (2), and adenomatous goiter (1). Patients ranged in age from 21 to 79 years, with a median age of 50 years. There were 17 females and 4 males.

Microscopically, TZs were composed of thyroid follicles (Fig. 2a). The border between the TZs and main thyroid tissues was distinct in 20 (95.2%) out of 21 cases, and continuous or discontinuous, thin fibrous connective tissue bundles were present at the boundary (Fig. 2b). The main thyroid tissue did not have any interlobular connective tissue. Histological findings from thyroid follicles in the TZ and main thyroid tissue were similar, except in 1 case, in which the size of the thyroid follicles in the TZ was slightly larger than that of those in the main thyroid (Fig. 3). Four cases showed mild chronic thyroiditis with oxyphilic changes in follicular cells and lymphocytic infiltration. In all these samples, the TZ also showed signs of chronic thyroiditis. Solid cell nests were found within the TZ in 1 case (4.8%), and within the main thyroid tissues in 3 cases (14.3%). The parathyroid glands and thy-

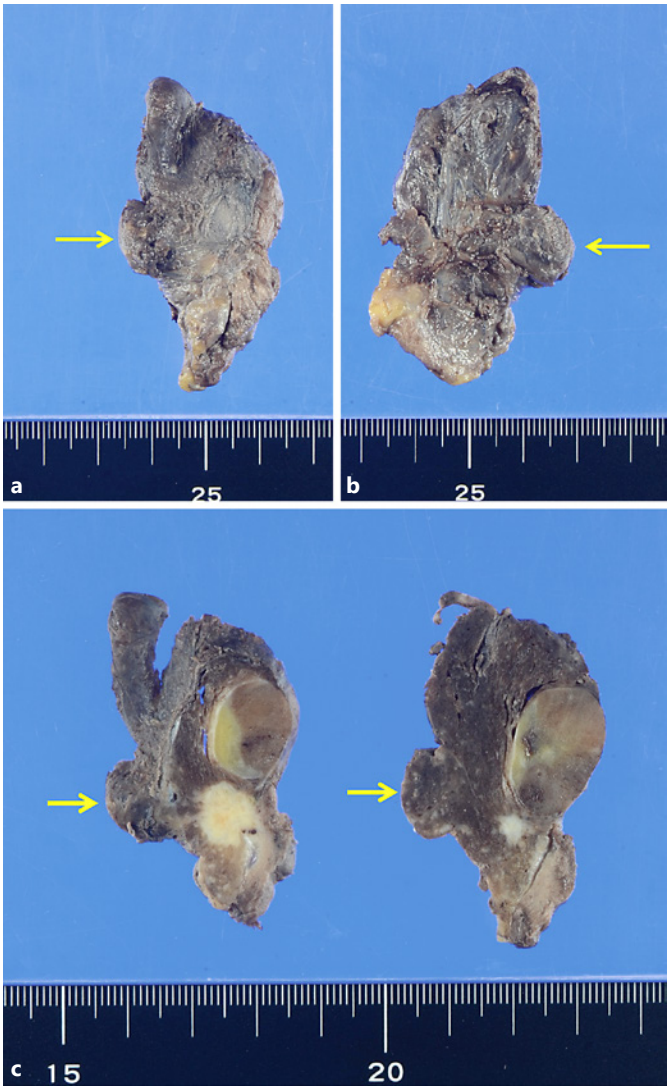

Fig. 1. Gross findings of the thyroid tubercle of Zuckerkandl, grade 3 (arrows). **a** Frontal view. **b** Dorsal view. **c** Cut surface. The case shown here involved a lobectomy to remove papillary thyroid carcinoma and follicular neoplasm.

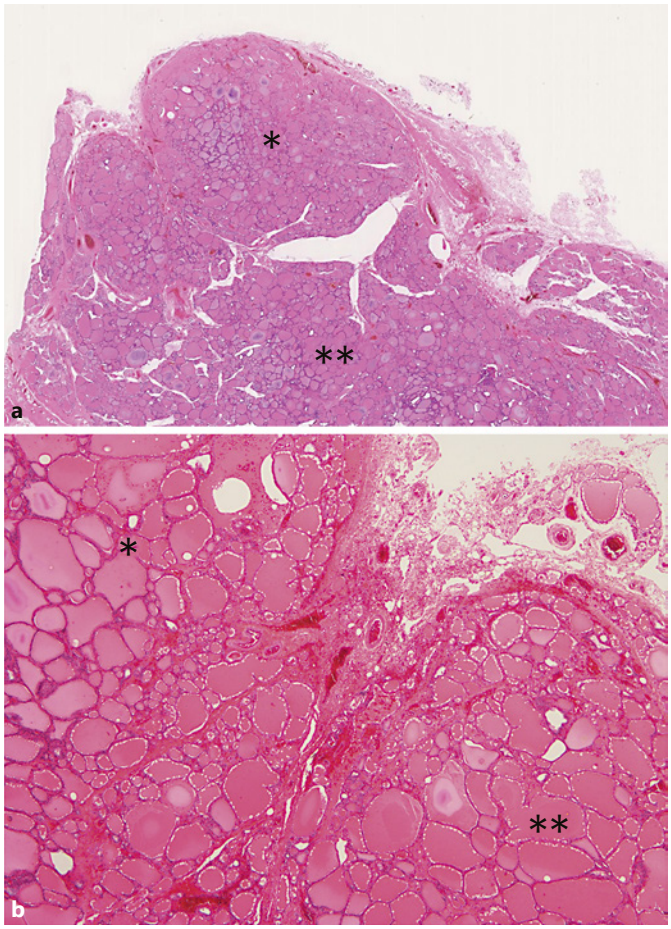

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Fig. 2. a Microscopic appearance of the thyroid tubercle of Zuckerkandl (TZ) (*) is similar to that of the main thyroid tissue (**). **b** Thin, fibrous connective tissue bundle is present between the TZ and main thyroid tissue.

mus were present within the perithyroid connective tissue in 4 cases (19.0%) and 1 case (4.9%), respectively.

Calcitonin-positive C cells were scattered within the TZ in 1 case (4.8%) (Fig. 4) and within the main thyroid tissue in 15 cases (71.4%) (Fig. 5). The number of C cells in the main thyroid tissue ranged from 5 to 37 (median 15.5) per high-power magnification field (×40 lens). The number of samples showing C cells in the TZ was significantly lower than that of samples showing C cells in the main thyroid tissue ($p < 0.0001$). In the case where C cells were found in the TZ, 7 and 15 calcitonin-positive cells were found in high-power magnification fields of the TZ and main thyroid tissue, respectively. C-cell distribution was random and did not show central or subcapsular restriction. There were no histological differences between cases with and without C cells or solid cell nests.

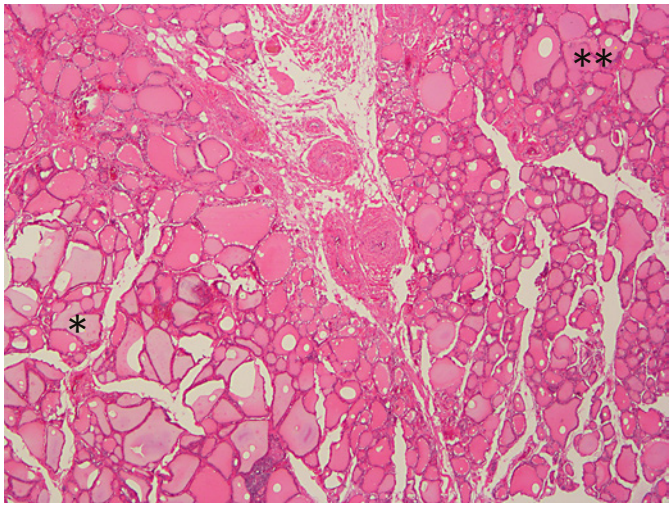

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Fig. 3. Thyroid follicles in the thyroid tubercle of Zuckerkandl (*) are larger than those in the main thyroid tissue (**).

Discussion and Conclusion

The TZ is the posterior extension of the thyroid lateral lobes or a protuberance from the posterolateral border of the thyroid lobe [1–8]. It is significantly more common in the right than in the left lobe [5, 7, 8, 11–13]. It is usually observed in the middle third of the thyroid lateral lobe (80–85%) and it can also be found in the lower part or in the upper third of the lobe [1]. In our study, 90.5% of TZs examined were located in the right lobe.

Pelizzo et al. [4] classified TZs into four grades based on size: grade 0, unrecognizable; grade 1, only a thickening of the lateral edge; grade 2, <1 cm; and grade 3, ≥1 cm. Previous studies have shown that grade 2 TZs seem to be the most common, although their frequency in different studies varied [3, 4, 7, 13], likely because it is unclear whether "size" indicates the length of the base or the height of the structure. In addition, TZs differ in shape or size depending on whether they are fresh or fixed [7]. The TZ is present in 60–83% of the patients undergoing thyroidectomy [1, 2, 5, 8, 10–13]. In this study, however, only 2.9% of the thyroidectomy cases were included. Since the examined cases were limited to lesions (grade 2 or 3) clearly recognized with the naked eye, the materials were collected from formalin-fixed thyroid tissue that obscured the lesions; left lobectomy cases were included among the selected cases.

Reports describing histological findings of TZs are few. Gurleyik and Gurleyik [21] reported 2 cases of TZs, describing the area as being composed simply of thyroid tissue. Microscopically, the TZ is comparable with other areas of the thyroid tissue [7]. Nodular lesions may develop

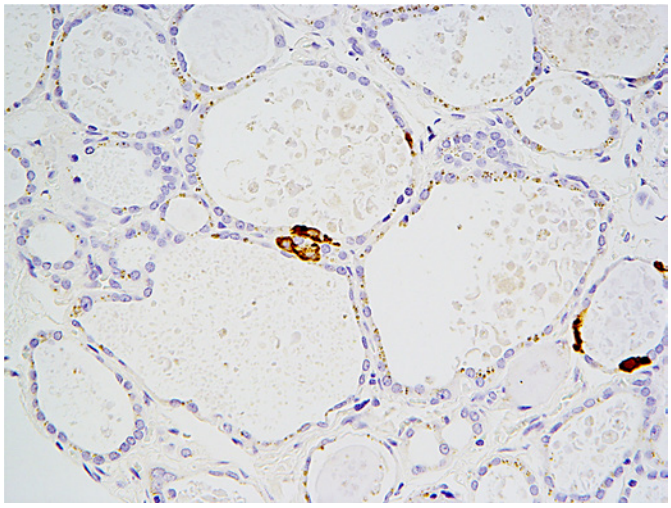

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Fig. 4. One case shows calcitonin-positive cells scattered in the thyroid tubercle of Zuckerkandl (immunostaining for calcitonin).

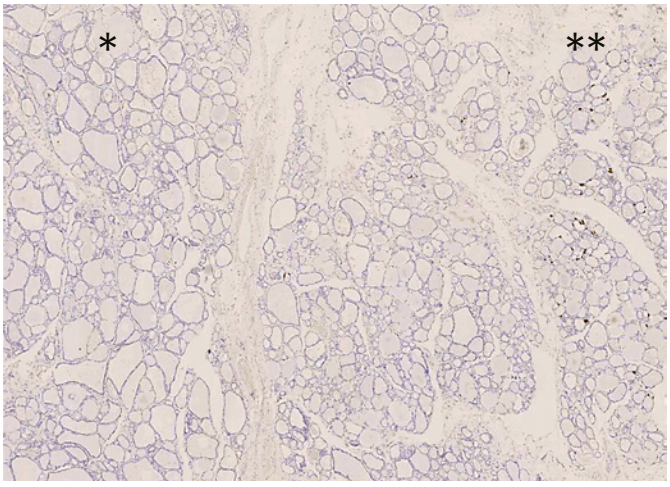

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Fig. 5. Calcitonin-positive cells present in the main thyroid tissue (**). The thyroid tubercle of Zuckerkandl (*) does not exhibit calcitonin-positive cells (immunostaining for calcitonin).

within the TZ just as in main thyroid tissues [22]. Our study findings are, in part, in agreement with others. We found TZs microscopically similar to the main thyroid tissue, except in 1 case where the thyroid follicles in the TZ were slightly larger than those in the main thyroid tissue. In 4 cases of chronic thyroiditis, both the TZ and main thyroid tissue showed chronic inflammatory cell infiltration and oxyphilic changes in follicular cells. We also saw no apparent microscopic difference between the TZ and main thyroid tissue in hematoxylin and eosin-stained sections. To our knowledge, our study is the first to describe the presence of thin fibrous connective tissue bundles at the border between the TZ and main thyroid tissue.

Anatomically, the thyroid is divided into lobules. There are 20–40 thyroid follicles in one lobule [23], but the TZs we examined contained considerably more lobules. In addition, the incidence of interlobular fibrous connective tissue was 8.0% in normal tissue [23], but it was 95.2% in TZs in our study. To clarify whether the thin fibrous connective tissue bundle is congenital or acquired, further examination, particularly of TZs from neonates or infants, is required.

According to previous reports, the TZ is the residual posterolateral projection from the lateral thyroid component, indicating the point of the embryologic fusion of the median anlage and the paired smaller lateral anlagen (UB) [5, 8, 11, 15–18]. Considering the current consensus on the origin of C cells, solid cell nests, and the TZ, the TZ should include C cells and solid cell nests, and their distribution in TZ should be denser than that in the main thyroid tissue. However, our results contradict the theory that the TZ is the remnant of the UB. We observed C cells within TZs in only 4.8% of the cases. Instead, they were more frequently observed within the main thyroid tissue (71.4%), where they were more densely distributed. Solid cell nests were found in 4.8% of the TZs and in 14.3% of the main thyroid tissues. Contradictory to our findings, Viveka [8] previously described the TZ as having a higher concentration of C cells. Vandernoot et al. [24] reported that C cells may be present in ectopic lingual thyroids that should not embryologically contain C cells. Therefore, the UB is not the only source of C cells. Mirilas and Skandalakis [15] described that medullary thyroid carcinoma develops from C cells that participate in the formation of the TZ, and Chevallier et al. [17] emphasized that primitive medullary thyroid carcinoma always develops from the TZ17]. However, as they did not show the data or photographs in detail, we cannot verify the findings. Additionally, the TZs predominated in the middle third of the lobe; most C cells usually exist in the upper third region [23].

Both C cells and solid cell nests arise from the UB. The piriform sinus fistula is a congenital branchial pouch abnormity that arises from the piriform sinus and ends in the upper and internal portions of the thyroid [25]. Miyauchi et al. demonstrated that an aggregation of C cells was present near the fistula and concluded that the fistula traces the migration route of the UB to the thyroid [25]. The intrathyroidal location of the piriform sinus fistula is not the TZ. The former is present in the upper third of the thyroid [25], whereas the latter is found in the mid-

dle third [1]. In addition, TZs more frequently appear in the right lobe [2, 5, 6, 10], whereas piriform sinus fistulae more frequently occur in the left lobe [25]. Taken together, this indicates that it is unlikely that the remnants of the UB are involved in the formation of the TZ.

Our study has a few limitations. This was a study on selected cases of TZs defined as grade 2 or 3 according to Pelizzo's grading system [7]. Smaller TZs or those of an earlier stage may not exhibit the same characteristics as those that we have seen here. In addition, the TZs we examined were identified only from fixed specimens.

Nevertheless, we have demonstrated two novel findings: (1) TZs are separated from the main thyroid tissue by thin, fibrous connective tissue, and (2) C cells and solid cell nests within TZs were less common than those within the main thyroid tissue. We believe that although the TZ may have an embryological development unique from that of other thyroid tissue, it is unlikely that the UB is involved in its formation. Modification to our current understanding of the composition and derivation of the TZ, however, will require additional research, by our group as well as others.

Statement of Ethics

The study protocol was approved by the Institutional Review Board of Kuma Hospital, Hyogo, Japan (approval No.: 20181011-2). Informed consent was obtained from the patients whose samples were used.

Disclosure Statement

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Author Contributions

Conceptualization and methodology, M.Higuchi; data preparation, M. Higuchi, M. Hirokawa, A. Suzuki; original draft preparation and writing, M.Higuchi; draft review and editing, M.Hirokawa, A. Miyauchi; supervision: M.Hirokawa, A. Miyauchi, H. Masuoka.

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