Pathologic features of polycystic thyroid disease: Comparison with benign nodular goiter

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Abstract. Polycystic thyroid disease (PCTD) is characterized by multiple thyroid cysts detected by ultrasonography, the absence of thyroid autoantibodies, and susceptibility to the development of hypothyroidism due to a high iodine intake. It is necessary to obtain histopathological information on PCTD in order to clarify the cause of hypothyroidism. We retrospectively reviewed three patients with PCTD and small papillary thyroid cancer who underwent thyroidectomy. We observed the thyroid tissues pathologically in areas with and without multiple cysts, and compared them with those of multinodular goiter with cysts. In the patients with PCTD, there were multiple enlarged follicles that resembled enlarged normal follicles and differed from those found in multinodular goiter in terms of their shape. Huge follicles corresponded to the cysts that were detected by ultrasonography. Each follicle contained colloid. Follicular cells in enlarged follicles comprised low cuboidal epithelium that appeared normal. These findings were common in the 3 patients with PCTD. In Conclusion the PCTD patients had multiple enlarged follicles that seemed to decrease the total number of follicular cells, and may be a cause of hypothyroidism. We believe that PCTD is a new entity of thyroid disease based on the pathological findings.

Key words: Hypothyroidism, Thyroid cyst, Polycystic thyroid diseases, Pathology

POLYCYSTIC thyroid disease (PCTD) is characterized by multiple thyroid cysts detected by ultrasonography, the absence of thyroid autoantibodies, and susceptibility to the development of hypothyroidism due to a high iodine intake [1]. We previously reported that hypothyroidism induced by PCTD accounted for about 7% of all causes of hypothyroidism in a region with a high iodine intake [2]. We speculated that the development of hypothyroidism was due to a decreased volume of normal thyroid hormone-producing tissue because of multiple cysts in PCTD. From the previously published images of ultrasonography, PCTD may have been classified as multinodular goiter thus far. We have to obtain histopathological information on PCTD in order to clarify whether it is different from multinodular goiter. We retrospectively identified three patients with PCTD who underwent thyroidectomy because of papillary thyroid carcinoma, and were able to obtain the PCTD tissues. We present the pathologic findings of PCTD in these patients and compare them with those of multinodular goiter with cysts in this report.

Subjects and Methods

The subjects were three PCTD patients who underwent thyroidectomy because of papillary thyroid carcinoma. Since the carcinomas in these patients were small, we were able to observe the non-carcinomatous thyroid tissues. As control cases, we collected seven cases with multinodular goiter macroscopically containing multiple cystic lesions, which were resected from 2007 to 2010 in our hospital. Serum thyroid hormone levels were normal in all control cases. We observed the tissues of cystic lesions and normal-looking areas in both groups.

Laboratory methods

TSH, FT4, and FT3 concentrations were measured employing chemiluminescent immunoassays
and had no family history of thyroid disease. She had hypertension and hyperlipidemia, under medical treatment, and a past history of total hysterectomy due to adenomyosis uteri. She consumed an average amount of seaweed as part of a regular diet. Thyroid function tests showed subclinical hypothyroidism with an elevated serum TSH level, at 23.2 µU/mL, FT4 at 0.78 ng/dL, and FT3 at 2.83 pg/mL. Serum Tg was 666.1 ng/mL. Her TSH level was normalized to 2.96 µU/mL with 50μg of levothyroxine one month later. Tests for TgAb and TPOAb were negative. Multiple thyroid cysts were observed in both lobes and a small, solid, hypo-echoic nodule was detected on the right lobe by ultrasonography (Fig. 1). The estimated volume of the thyroid on ultrasonography was 37 mL. Cytology of a fine-needle aspiration biopsy specimen obtained from the solid hypo-echoic nodule on the right lobe demonstrated papillary thyroid carcinoma. Consequently, the patient underwent total thyroi-
Pathologic features of PCTD

All three patients had no cystic diseases of other organs based on an interview.

**Pathologic findings**

**Patient 1**

Resected thyroid revealed solid tumor and multiple cystic lesions (Fig. 2A). The former was papillary thyroid carcinoma, which was consistent with the small, solid, hypo-echoic nodule on ultrasonography. Each follicle contains colloid in patient 1 (hematoxylin and eosin). Cystic follicles are cuboidal or low columnar, and are larger than those of the surrounding normal follicles in patient 1 (High-power field). D, E: Unilocular cystic dilatation of the thyroid follicles are seen. (D: patient 2, E: patient 3)

**Patient 3**

A 64-year-old man was referred to our hospital because of an abnormal accumulation in the thyroid right lobe on positron emission tomography. He was asymptomatic and had no family history of thyroid disease. He had a past history of multiple cancers including left renal cancer, gastric cancer, lung cancer, skin cancer on the little toe of the right leg, and bladder cancer. He ate seaweed every day. Thyroid function tests showed hypothyroidism with an elevated serum TSH level, at 23.129 µU/mL, and FT4 at 0.64 ng/dL. Serum Tg was 233.1 ng/mL. His TSH and FT4 levels improved to 5.658 µU/mL and 0.92 ng/dL, respectively, with 50µg of levothyroxine one month later. A test for TgAb was negative. Multiple thyroid cysts were observed in both lobes and a small, solid, hypo-echoic nodule was detected on the right lobe by ultrasonography (Fig. 1). On the cytological analysis of a fine-needle aspiration biopsy specimen obtained from the solid hypo-echoic nodule on the right lobe, a poorly differentiated carcinoma or metastatic carcinoma was suspected. Consequently, the patient underwent total thyroidectomy and central lymph node dissection.

All three patients had no cystic diseases of other organs based on an interview.
icles of variable sizes throughout most of both lobes. The microscopic findings of the cystic follicles were similar to those obtained in patient 1 (Fig. 2D).

**Patient 3**

Pathology of the small, solid, hypo-echoic nodule on ultrasonography was papillary carcinoma. Multiple enlarged follicles were seen in both lobes. The microscopic findings were similar to those obtained in patients 1 and 2 (Fig. 2E).

**Control cases**

Microscopically, multinodular goiters with cystic component were examined. Large cystic nodules revealed papillary projections containing small follicles, which is characteristic of this lesion and called Sanderson polster (Fig. 3), except for a small cystic follicle in one case.

**Comparison of normal-looking thyroid tissue**

The size of thyroid follicles seen in thyroid tissue without cystic change was apparently different between PCTD and multinodular goiter. The thyroid follicles seen in cases with PCTD were two to three times larger than those of multinodular goiter patients (Fig. 4 A, B).

**Discussion**

Typical multinodular goiter shows varied patterns consisting of large and small follicles. Giant follicles in adenomatous nodules are often irregular in shape and formed by cystic degeneration. The cysts in the present patients with PCTD were different from those found in adenomatous nodules in terms of their shape. Most

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**Fig. 3** Pathologic findings of multinodular goiter with multiple cystic lesions. Large cystic follicles revealed papillary projections containing small follicles, characteristic of this lesion and called Sanderson polster (hematoxylin and eosin).

**Fig. 4** Normal-looking follicles without cystic change. A-1, 2, 3: Multinodular goiter. B-1, 2, 3: PCTD. (B-1: patient 1. B-2: Patient 2. B-3: Patient 3.) The normal-looking follicles in the tissues of PCTD patients were two to three times larger than those of multinodular goiter patients (hematoxylin and eosin). Photographs are taken under the same magnification.
of the cysts were round, and even the large cysts resembled enlarged normal follicles. Surprisingly, the size of normal-looking follicles without cystic change in the tissues of PCTD patients was larger than those of multinodular goiter patients. These pathological features were identified in all the presented cases with PCTD, and may be the cause of PCTD. We previously reported that the tissue between the cysts detected by ultrasound was hypo-echoic and had a sponge-like appearance in the PCTD patients [1]. The huge follicles seemed to be cysts and the area with moderately large follicles appeared as hypoechoic lesions on ultrasound.

If we assume that a large sphere represents a thyroid lobule and a small sphere represents a single follicle, the surface area of a small sphere represents the number of follicular cells in a single follicle. The number of small spheres (radius: r) in a large sphere (radius: R) is approximated by the formula: \(\frac{4}{3}\pi R^3 = \frac{4}{3}\pi r^3\). The total surface area of small spheres in a large sphere is approximately \(\frac{4}{3}\pi R^3 \div \frac{4}{3}\pi r^3 \times 4\pi r^2 = 4\pi R^2/r\). This means that when the radius of a small sphere doubles in size, the total surface area of small spheres decreases by half in the same large sphere. When the radius of a small sphere increases, the total capacity for thyroid hormone production in PCTD may decrease because the total surface area of small spheres represents the number of follicular cells in thyroid. Although thyroid volumes slightly increased in the patients with PCTD, compensatory thyroid hormone production may not be sufficient, especially with a dietary iodine excess.

The capacity for thyroid hormone production depends on the number of follicular cells and functional capability of each cell. Although we cannot measure the function of follicular cells, we can estimate it based on the morphology of follicular cells to some extent. High cuboidal epithelium that is shown in Graves’ disease suggests the hyper-function of follicular cells. Since the height of the cuboidal epithelium appeared normal in the patients with PCTD, we speculate that the follicular cells in PCTD are not hyper-functioning. Therefore, a decreased number of follicular cells may be a cause of hypothyroidism and sensitivity to iodine excess, similarly to patients who undergo partial thyroidectomy for benign thyroid nodules [3].

There was an interesting report about the histological study of iodine-induced hypothyroidism from Japan [4]. The authors studied thyroid specimens obtained from 28 patients with iodine-induced hypothyroidism by using percutaneous needle biopsy. They found common histological changes thought to be specific for iodine-induced hypothyroidism; hyperplastic change in the follicles with some papillary folding, cuboidal to columnar change of follicular cells with clear and vesicular cytoplasm, scanty or absent colloid material in the large distended follicles, and occasional dilatation of capillary vessels. Follow up biopsy was performed in the euthyroid phase after iodine restriction in 2 patients, they found no histological changes seen in the hypothyroid phase. Fifteen of the 28 specimens showed no lymphocytic infiltration. They suggested the possibility that the patients with iodine-induced hypothyroidism may have a multinodular goiter as the underlying disease. We do not know whether these patients had thyroid cysts or not because they did not mention ultrasonography. There is a possibility that the reported patients without lymphocytic infiltration can correspond to PCTD. However, there is a difference between our cases and theirs. While our cases were operated when they became euthyroid, needle biopsies were performed during hypothyroid phase in their cases. Pathologic features of PCTD that we found seem to be irreversible.

Multinodular goiter is a composite disease, in which nodules are formed in the thyroid due to various causes. Multinodular goiter will be classified as various diseases in the future. Though multinodular goiter was one of the rare causes of hypothyroidism in our previous report, PCTD was more common as the cause of hypothyroidism [2]. The pathological findings of PCTD presented in this report confirmed that PCTD is a new entity of thyroid disease, which can be distinguished from multinodular goiter. It is well known that most of the patients with iodine-induced hypothyroidism have underlying thyroid diseases. Markou et al. suggested that iodine-induced hypothyroidism does occasionally occur in normal individuals but is exceedingly rare [5]. PCTD should be recognized as the underlying cause of iodine-induced hypothyroidism.

In summary, we presented pathological findings of the thyroid in 3 patients with PCTD. There were multiple enlarged follicles that resembled enlarged normal follicles and differed from those found in multinodular goiter in terms of their shape. The patients with PCTD had multiple enlarged follicles that seemed to decrease the total number of follicular cells, and this may be a cause of hypothyroidism. We believe that PCTD is a new entity of thyroid disease.
References


