Pendred syndrome (OMIM 274600) is an autosomal recessive disorder characterized by sensorineural deafness, a partial defect in iodide organification, and dyshormonogenetic goiter. Several cases of Pendred syndrome with follicular thyroid carcinomas were reported previously. Here we report identical twin patients with Pendred syndrome, who had thyroid tumors with distinct histopathological findings. 34-year-old identical twins with congenital deafness and goiter were referred to our hospital with complaint of neck discomfort. The genetic testing showed that these twin patients were compound heterozygotes carrying the same two mutations in the Pendred’s syndrome (PDS / SLC26A4) gene (c2168A>G and ins2110GCTGG), which confirmed the diagnoses of Pendred syndrome. They underwent thyroidectomy. Histological examination of the thyroid tumors resected from these twin patients revealed follicular variant of papillary thyroid carcinoma, and diffuse and nodular goiter without any evidence of malignancy, respectively. To our knowledge, the former is the first case of follicular variant of papillary thyroid carcinoma in Pendred Syndrome.

Key words: Pendred syndrome, Papillary carcinoma, Multinodular goiter, Dyshormonogenetic goiter

PENDRED SYNDROME (OMIM 274600) is an autosomal recessive disorder characterized by sensorineural deafness, goiter, and a partial defect in iodide organification. This syndrome was first described by Vaughan Pendred in 1896 [1]. Its molecular cause was elucidated by demonstrating biallelic mutations in the Solute Carrier 26A4 (SLC26A4) gene, also referred to as Pendred’s syndrome (PDS) gene, which encodes pendrin, a multifunctional anion transporter. Expression of pendrin has been documented predominantly in the thyroid, the inner ear, and the kidney, but also in a few other tissues [2].

In the thyroid gland, pendrin is located at the apical surface of the thyroid cell and functions as a chloride-iodide transporter [3]. Iodine is transported by pendrin from the cell to the colloid in the follicular lumen, and binds to tyrosine residues of thyroglobulin [4]. The loss of pendrin function results in an organification defect and can lead to dyshormonogenetic goiter [5]. Dyshormonogenetic goiters are an important clinical challenge as they may undergo malignant transformation probably due to prolonged stimulation by thyrotropin. In Pendred syndrome, the incidence of thyroid cancer is estimated to be about 1% [6]. The most common histology of the thyroid cancers arising from dyshormonogenetic goiters in patients with Pendred syndrome was follicular carcinomas [6].

Here we report unique cases of identical twin patients with Pendred syndrome who had thyroid tumors with distinct histology; follicular variant of papillary thyroid carcinoma, and diffuse and nodular goiter without any evidence of malignancy, respectively.
Results

Case Reports

Patient II-3

A 34-year-old man with congenital deafness (patient II-3 in Fig. 1) was referred to our hospital because of neck discomfort and difficulty in swallowing. He was born as the biovular triplet with patient II-2 and individual II-4 to non-consanguineous parents (individual I-1 and I-2), as shown in Fig. 1. He and patient II-2 are identical twins (Fig. 1). His parents (individual I-1 and I-2) and two siblings (II-1 and II-4) have normal hearing and no thyroid goiters. He had congenital deafness, but his growth and development were otherwise normal.

He had a large multinodular goiter. His thyroid function tests revealed a normal level of free triiodothyronine (fT3; 3.98 pg/mL, normal range 2.97-4.51 pg/mL), a decreased level of free thyroxine (fT4; 0.48 ng/dL, normal range 0.82-1.59 ng/dL) and a normal level of thyrotropin (TSH; 1.83 µU/mL, normal range 0.43-3.94 µU/mL). The normal level of thyrotropin may result from a normal level of free triiodothyronine despite the lower level of free thyroxine. Thyroglobulin was markedly increased (>800 ng/mL; normal range <30 ng/mL). Anti-thyroid peroxidase antibodies (Abs), anti-thyroglobulin Abs, and anti-TSH receptor Abs were all negative. Thyroid ultrasonography demonstrated a 30 × 23 × 32 mm isoechoic nodule in the left lobe. Ultrasound-guided fine-needle aspiration (FNA) cytology of the left lobe was performed. Cytological examination was consistent with a benign nodule. Substitution therapy with L-thyroxine was started immediately, and then the thyroid function test showed normal levels of free triiodothyronine (fT3; 3.8 pg/mL, normal range 2.97-4.51 pg/mL), free thyroxine (fT4; 1.05 ng/dL, normal range 0.82-1.59 ng/dL) and thyrotropin (TSH; 0.904 µU/mL, normal range 0.43-3.94 µU/mL).

At the age of 37, thyroid ultrasonography (Fig. 2A) showed that the size of the nodule in the left lobe was growing (43 × 41 × 28 mm). Ultrasound-guided FNA cytology showed findings consistent with papillary carcinoma. The lesion except for the nodule in the left lobe showed the multiple nodular goiter (Fig. 2B). Subsequently a total thyroidectomy with lymph nodes dissection was performed.

Patient II-2

The patient II-2 had also congenital deafness, but

Fig. 1 Pedigree of the family with the PDS gene mutations

Patient II-3 (the proband), patient II-2 and individual II-4 are the biovular triplet. Moreover, patient II-3 and patient II-2 are identical twins. Filled symbols represent Pendred syndrome. Circles represent females, squares represent males, and half-filled symbols represent heterozygous carriers. The index patient II-3 with Pendred syndrome and papillary carcinoma is designated with an arrow.

Fig. 2 Thyroid ultrasonography of the patient II-3 at the age of 37 years

(A) A growing isoechoic nodule (43 × 41 × 28 mm) in the left lobe and (B) the lesion of the multiple nodular goiter.
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his growth and development were otherwise normal. He complained about neck discomfort at the age of 34. He had a large multinodular goiter. Thyroid ultrasonography demonstrated a nodule in the right lobe. Ultrasound-guided FNA cytology of the right lobe was performed. Cytological examination was consistent with a benign nodule. Three years later, he complained of difficulty in swallowing at the age of 37. His thyroid function tests at that time revealed normal levels of free triiodothyronine (fT3; 3.46 pg/mL, normal range 2.97-4.51 pg/mL), free thyroxine (fT4; 1.17 ng/dL, normal range 0.82-1.59 ng/dL), and thyrotropin (TSH; 1.09 µU/mL, normal range 0.43-3.94 µU/mL). Thyroglobulin was markedly increased (587 ng/mL; normal range <30 ng/mL). Anti-thyroid peroxidase Abs, anti-thyroglobulin Abs, and anti-TSH receptor Abs were all negative. Thyroid ultrasonography showed no significant change in the size of the nodule in the right lobe when compared to that at the age of 34. Ultrasound-guided FNA cytology of the nodule in the right lobe was consistent with a benign nodule. Subsequently a total thyroidectomy was performed because of the difficulty in swallowing.

Genetic testing

The genetic testing of the PDS gene was performed in the twin patients (II-2 and II-3) before surgery of the thyroid gland with their family (Fig. 3). This study was approved by the ethical committees of KKR Suifu Hospital and Dokkyo Medical University. Informed consent was obtained from each subject. The patients II-2 and II-3 were found to be compound heterozygotes for two mutations in the PDS gene, confirming the diagnosis of Pendred syndrome. The first mutation was a frequently found transversion A→G at position 2168 of the cDNA sequence (c2168A>G), resulting in a predicted His→Arg substitution at residue 723 (H723R) (Fig. 3A). The second mutation was a five-nucleotide insertion of GCTGG in exon 19 causing a frameshift leading to an amino-acid sequence change from codon 704, followed by a stop at codon 722 (Fig. 3B). The
individual I-1 and the II-4 were heterozygous for the first mutation. The individual I-2 and the II-1 were heterozygous for the second mutation.

Pathological findings of the thyroid glands in patients II-3 and II-2

The weight of the resected thyroid was 482 g in patient II-3 and 560 g in patient II-2, respectively. The surface of the macroscopic specimen from patient II-3 showed the existence of multinodular goiter (Fig. 4A). Figure 4B shows the gross cut surface of the nodule in the left lobe of patient II-3. Microscopic examination of this thyroid nodule showed encapsulated follicular lesion (Fig. 5A), with nuclear grooves (Fig. 5B, 5C, 5D) and an intranuclear cytoplasmic inclusion (Fig. 5B, 5C, 5E), which are the findings consistent with a follicular variant of papillary thyroid carcinoma.

There was no evidence of capsular invasion, vascular invasion, lymphatic invasion, or metastases in local regional lymph nodes. The remainder of the gland showed the multiple benign nodules. The examination of the resected tumor showed that BRAF point mutations [7] were negative in the patients II-3.

Macroscopic findings of the thyroid gland from patient II-2 also showed the existence of multinodular goiter (Fig. 4C) with a nodule of 8 x 6 mm (Fig. 4D). In contrast to the patient II-3, the histological examination of the nodule in the right lobe from the patient II-2 showed fibrotic change without evidence of malignancy (Fig. 5F, 5G). The remainder of the gland showed the multiple benign nodules.

Discussion

Pendrin transports iodide from the thyroid follicular cell to the colloid in the follicular lumen. The loss of pendrin function results in an iodide organification
defect, and often in the development of dyshormonoge-
netic goiter [5]. The most common histological type of
the thyroid cancer arising from dyshormonogenetic goi-
ters consisted of follicular carcinomas [8]. By contrast,
the pathological diagnosis of the patient II-3 was folli-
cular variant of papillary thyroid carcinoma. Yashiro et
al. and Hishinuma et al. reported cases of papillary car-
cinoma in association with dyshormonogenetic goiter,
who did not have Pendred syndrome however [9, 10].
There have been several case reports on patients with
Pendred syndrome who developed thyroid follicular
carcinomas [11-16], but no reports on papillary thyroid
carcinoma among patients with Pendred syndrome. To
the best of our knowledge, the patient shown in the
present paper is therefore the first case of papillary thy-
roid carcinoma in a patient with Pendred syndrome.

Fig. 5  Histopathology of the thyroid tumors in the patient II-3 (A, B, C, D, E) and the patient II-2 (F, G)
(A) The thyroid tumor from the patient II-3 showed encapsulated follicular lesion (hematoxylin and cosin (HE) stain). (B) The thyroid tumor from the patient II-3 showed histological feature of follicular variant of papillary carcinoma (HE stain). (C) Higher magnification of B. (D, E) Higher magnification of C. Features consistent with papillary carcinoma, such as nuclear changes (nuclear grooves (B, C, D) indicated by arrows and an intranuclear cytoplasmic inclusion (B, C, E) indicated by an arrowhead) were found in the tumor tissue of the patient II-3. (F) The thyroid nodule from the patient II-2 (indicated by the square in Fig. 4D) showed histological feature of fibrotic change (HE stain). (G) Normal follicular epithelial cells were observed in the thyroid gland of the patient II-2. Any atypical follicular epithelial cells were not found in it (HE stain).
The mechanisms underlying thyroid cancer development in dyshormonogenetic tissues are unknown. It has been proposed that long-standing elevated plasma levels of thyrotropin is one of the main causes for development of thyroid carcinoma arising from dyshormonogenetic goiter [17]. In the patient II-3, high thyrotropin levels were never documented, however, during the regular follow-up period, and therefore, cannot explain for development of thyroid papillary carcinoma in this case.

Generation of H$_2$O$_2$ is inhibited by iodine in the thyroid gland, and low iodine level may activate H$_2$O$_2$ generation, which could result in DNA and somatic mutation [18]. Furthermore, organic iodo-compounds have been shown to inhibit thyroid epithelial cell proliferation [19]. In addition to Pendred Syndrome, patients with iodide organization defect, such as thyroid peroxidase (TPO) mutation, are likely to develop thyroid carcinomas. Medeiros-Neto et al. and Chertok Shacham et al. reported cases of thyroid follicular carcinomas in patients with TPO mutations [20, 21]. Moreover, expression of several key proteins involved in thyroid iodide metabolism, such as thyrotropin receptor [22], thyroid peroxidase [23] and sodium iodine symporter [22], is frequently found to be reduced or absent in thyroid carcinomas. Iodide organization defect and increased oxidative stress in the thyroid gland of patients with Pendred Syndrome may partly explain the cause for the development of thyroid carcinoma.

In addition, aberrant gene promoter hypermethylation, which is a common mechanism for gene silencing in malignancy, may be responsible for the tumorigenesis of thyroid carcinomas. Xiang et al. [24] reported aberrant hypermethylation of the Pendred syndrome gene SLC26A4 in 44% of histologically benign adenomas, 46% of follicular thyroid cancers, 71% of papillary thyroid cancers, 71% of anaplastic thyroid cancers, and 100% of thyroid cancer cell lines, and suggested that aberrant methylation of the SLC26A4 gene was an early event in thyroid tumorigenesis.

The genetic background of the patient II-2 and the patient II-3 was identical. Only in the patient II-3, however, the multinodular goiter developed into a papillary carcinoma. Histopathological findings of the patient II-2 demonstrated no evidence of malignancy. Many factors, such as epigenetic and environmental factors, might be associated with the progression from thyroid goiter to cancer in Pendred syndrome.

In summary, we report identical twin patients with Pendred syndrome, one of whom developed follicular variant of papillary thyroid carcinoma. To our knowledge, this is the first case of follicular variant of papillary thyroid carcinoma in Pendred Syndrome. Further studies are required to elucidate the mechanisms of occurrence of carcinoma from thyroid dyshormonogenetic goiter in Pendred syndrome. Moreover, our case suggests that regular follow-up by using thyroid imaging is mandatory in patients with Pendred syndrome.

**Disclosure Statement**

The authors declare that no competing financial interests exist.

**References**

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