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Papillary thyroid carcinoma arising from a thyroglossal duct cyst: a single institution experience

Yun Mi Choi¹⁾, Tae Yong Kim¹⁾, Dong Eun Song²⁾, Suck Joon Hong³⁾, Eun Kyung Jang¹⁾, Min Ji Jeon¹⁾, Ji Min Han¹⁾, Won Gu Kim¹⁾, Young Kee Shong¹⁾ and Won Bae Kim¹⁾

¹⁾Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul 138-736, Korea

²⁾Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul 138-736, Korea

³⁾Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul 138-736, Korea

Abstract. Thyroid cancers arising from a thyroglossal duct cyst (TGDC) are rarely reported. No clear consensus exists regarding optimal management. In this light, TGDC carcinomas recently treated at Asan Medical Center, as well as previously reported cases in the literature, were reviewed. There were ten patients who were diagnosed with TGDC carcinoma at our institution. All patients underwent pre-operative fine-needle aspiration biopsy (FNAB). Nine patients were suspected of having papillary carcinoma following cytology. The Sistrunk operation (SO) was performed in four patients, SO with total thyroidectomy (SO/TT) was performed in three patients, and SO/TT with neck dissection was performed in three patients. Six patients who received total thyroidectomy underwent radioactive iodine (RAI) therapy and T4 suppression. With a median follow-up period of 28.5 months, two patients showed recurrence and one of them died of the disease. We analyzed 163 cases from 1990 to 2012 with three or more cases TGDC carcinoma, including the present study. Among 48 patients who underwent FNAB, 75% had papillary thyroid carcinoma (PTC). SO, SO/TT, or SO/TT with neck dissection was performed in 27%, 41%, and 32% of patients, respectively. Among 119 patients who received total thyroidectomy, 36% had concomitant PTC in the thyroid. Among 52 patients who received neck dissection, 69% had cervical nodal involvement. The results of our review suggest that when TGDC carcinoma is suspected, ultrasonography and, if necessary, FNAB should be performed. If these tests reveal a suspected lesion in the thyroid or lymph node, SO/TT and lymph node dissection should be performed.

Key words: Thyroglossal cyst, Thyroid neoplasms, Fine-needle biopsy

A THYROGLOSSAL DUCT CYST (TGDC), which is found in approximately 7% of the population, originates from the persistent tract formed during migration of the rudimentary thyroid gland between the base of the tongue and the anterior cervical region [1, 2]. It is the most common of the congenital anomalies of the neck and represents over 75% of childhood mid-line neck masses [3, 4]. Malignant changes in a TGDC are very rare, occurring in less than 1% of cases [5-7]. Approximately 250 cases of TGDC carcinoma have been published in the literature, mainly as single case reports or small case series [1, 8]. The median age for TGDC carcinoma is approximately 40 years of age and

it shows female predominance [5, 6].

It was generally known that the Sistrunk operation (SO) is the usual recommended treatment for TGDC carcinoma [5, 7]. The cure rate for papillary thyroid carcinoma (PTC) in TGDC has been reported as 95% when treated by SO [2, 5]. Furthermore, in a recent publication, the survival rate was reported as 100% when treated by SO/TT with lymph node dissection [1]. The surgical extent and the use of post-operative radioactive iodine (RAI) therapy remain controversial [4]. Recently, the concept of stratification by risk has been proposed to identify patients who would benefit from more aggressive treatment, *i.e.* total thyroidectomy and/or neck dissection and RAI therapy [1, 9, 10].

The aims of this study were to report the experience of our center with TGDC carcinoma over the last 15 years and to provide a review of previously reported cases from the literature.

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Correspondence to: Tae Yong Kim, M.D., Ph.D., Department of Internal Medicine, Asan Medical Center, 88, Olympic-Ro 43-Gil, Songpa-gu, Seoul 138-736, Korea. E-mail: tykim@amc.seoul.kr

Patients and Methods

Ten patients were diagnosed with TGDC carcinoma, confirmed by pathology, at Asan Medical Center between 1997 and 2011. A retrospective review of the clinical records of these ten patients was performed. Information collected included demographics, diagnosis, treatments, and outcome details.

A Medline search restricted to literature written in English and case reports including three or more patients between 1990 and May 2012, was conducted. One hundred and sixty-three cases, including the ten cases of our institution, were reviewed. We analyzed the extent of surgery, the use of RAI therapy, post-operative histopathologic results (thyroid or lymph node involvement), and recurrence and mortality rates.

The Ten Cases at Asan Medical Center (Table 1)

Baseline clinical characteristics

The patients were aged between 28 and 79 years old (median 54 years). Two patients were male, and eight patients were female. None of the patients reported any

predisposing factors such as previous neck irradiation. Eight patients presented with a palpable midline neck mass and two patients had an impalpable mass that was detected by ultrasonography (Patient #7 and #10). Patient #7 was diagnosed through regular check-up. Patient #10 was diagnosed during follow-up for a previously known PTC in the thyroid. She was initially referred from another hospital for surgery. There was no description of TGDC carcinoma in her records. We did not perform additional ultrasonography and proceeded directly to lobectomy. Her first post-operative follow-up ultrasonography, 10 months after the initial surgery, revealed a malignant looking 1.8 cm solid and cystic mass at the hyoid bone level.

Pre-operative diagnosis by imaging modality and fine-needle aspiration biopsy

Six patients (Patient #2, #3, #6, #7, #8, and #10) underwent pre-operative ultrasonography. Eight patients (Patient #1 to #7, and #9), including four patients who did not undergo ultrasonography, received a neck computed tomography (CT) scan.

Eight patients showed a cystic mass with an internal solid portion in ultrasonography or CT. Among them,

Table 1 Clinicopathologic and follow-up information of the ten patients with thyroglossal duct cyst carcinoma treated at Asan Medical Center

No.	Age/ Sex	Preop w/u	Preop FNAB	Type of operation	LN dissection	Maximal tumour diameter (cm)	Cyst wall invasion	PTC in thyroid	Resection margin	N stage*	RAI (GBq)	T4 sup- pression	F/U (month)
1	25/F	CT	negative	SO	ND	0.6	+	-	Clear	pN0	ND	ND	25, NED
2	32/F	US/CT	suspicious†	SO	ND	1	+	-	Clear	pN0	ND	+	32, NED
3	37/M	US/CT	suspicious	SO	ND	1.2	-	-	Clear	pN0	ND	ND	18, NED
4	55/F	CT	suspicious	SO/TT	ND	1	-	+	Clear	pN0	3.7	+	165, NED
5	63/F	CT	positive	SO/TT	ND	1.2	-	+	Clear	pN0	2.8	+	153, NED
6	72/F	US/CT	positive†	SO/TT	CCND	1.5	-	-	Clear	pN0	1.1	+	18, NED
7	54/F	US/CT	positive†	SO/TT	CCND/ MRND	2.1	+	-	Involved	pN1b	5.6	+	4, NED
8	68/F	US	positive	SO/TT	CCND	4.5	+	-	Involved	pN1a	5.6	+	110, recur
9	55/M	CT	positive	SO/TT	ND	4.5	+	-	Involved	pN0	5.6	+	49, expire
10	59/F	US	positive†	SO	ND	0.9	-	-	Clear	pN0	ND	ND	7, NED

w/u, work-up; US, ultrasonography; CT, computed tomography; FNAB, Fine-needle aspiration biopsy; S, Sistrunk operation; TT, Total thyroidectomy; ND, Not done; CCND, Central compartment node dissection; MRND, Modified radical neck dissection; NED, No evidence of disease. * According to AJCC seventh edition (2010). † US guided FNAB.

five patients (Patient #1, #3, #6, #7, and #10) showed calcification (Patient #7 and #10 showed micro-calcification), suggesting malignancy. Two patients (Patient #4 and #5) did not show any findings suggestive of malignancy in ultrasonography or CT scan.

All patients underwent fine-needle aspiration biopsy (FNAB) of their midline neck mass. Four patients underwent ultrasonography-guided FNAB and six patients underwent manual FNAB. FNAB revealed a pre-operative diagnosis of TGDC carcinoma in all patients except Patient #1. The FNAB result from Patient #1 suggested a benign mass. She was diagnosed with a simple TGDC and only SO was performed.

Surgical extent

The extent of surgery varied individually according to the pre-operative imaging work-up. SO only was performed in four patients (Patient #1, #2, #3, and #10). SO with total thyroidectomy (SO/TT) was performed in three patients (Patient #4, #5, and #9). Only Patient #4 had thyroid nodule on CT scan. There were three patients who had suspicious lymph nodes seen in their pre-operative ultrasonography examination (Patient #6, #7 and #8). SO/TT with central compartment node dissection (CCND) was performed in two patients (Patient #6 and #8). SO/TT with CCND/modified radical neck dissection (MRND) was performed in one patient (Patient #7).

Post-operative pathological diagnosis

All ten patients had papillary carcinoma. The tumor size ranged from 0.6 to 4.5cm. Two patients had concomitant PTC in the thyroid gland and they showed multifocal papillary carcinoma in both thyroid lobes. Another two patients had cervical nodal involvement.

Adjuvant treatment after surgery

All six patients who received total thyroidectomy underwent adjuvant RAI therapy and T4 suppressive therapy.

Follow-up

All patients have regular check-ups with ultrasonography every 1-2 years. Two patients (Patient #8 and #9) showed recurrence with a median follow-up of 28.5 months (range 7-165 months). One of these patients developed multiple distant metastasis, including brain metastasis and died of the disease.

Patient #8 received total thyroidectomy with bilat-

eral CCND and post-operative RAI therapy (5.55GBq). Recurrence in operation bed was detected by ultrasonography 9 years after the initial operation. She underwent excision of the locally recurrent tumor and remains free of disease 7 months after the reoperation.

Patient #9 developed distant metastasis. A post-therapeutic whole body scan (RxWBS) revealed diffuse lung metastasis. He underwent three additional sessions of RAI therapy (cumulative dose of 22.2GBq). However, a persistent neck mass was still growing for 31 months. He underwent excision and selective neck node dissection (II-IV, Right) 33 months after the initial surgery. One year after the second operation, he visited the emergency room with an altered mental state. Brain CT and magnetic resonance imaging (MRI) revealed a large 8 x 5 cm sized hemorrhagic mass in the left frontal lobe, highly suggestive of brain metastasis. A chest CT revealed multiple metastatic nodules in both lungs. He refused further treatment and died of the disease 49 months after the initial surgery.

Review of the Literature (Table 2)

We reviewed 163 cases in the literature, including the ten cases from the Asan Medical Center [1, 4-24]. Fifty-six patients were male. Patients were aged between 14 and 76 years (mean 41.2) years. Forty-eight patients underwent FNAB, and among them, 75% of patients were suspected as having PTC by cytology. SO only, SO/TT, or SO/TT with neck dissection was performed in 27%, 41%, and 32% of patients, respectively. This result was unexpected given that the usual treatment for TGDC carcinoma is SO. In fact, SO/TT was the most commonly performed treatment modality. RAI therapy was administered in 57% of patients. Among 119 patients who received total thyroidectomy, 36% showed concomitant PTC in the thyroid. Among 52 patients who received neck dissection, 69% had cervical nodal involvement. Sixteen (10%) among 163 patients had recurrence of their disease. Most patients presented with local recurrence except for four patients who presented with lung metastasis. Two patients died of the disease.

Discussion

TGDC carcinoma typically presents as a midline palpable neck mass. Malignancy should be suspected if the cyst is hard, fixed, irregular, or displays sudden expan-

Table 2 Review of previous literature including 153 cases of thyroglossal duct cyst carcinoma

Year of publication	First author	No of cases	FNAB	SO	SO/TT	SO/TT with neck dissection	thyroid involve	LN involve	Distant metastasis	RAI	recurrence	Disease-related death
1991	Pacheco-Ojeda L [11]	5	0/1	3	0	2	1	1	0	0	1	0
1991	Fernandez JF [12]	10	NA	5	2	3	2	0	0	5	0	0
1992	Maziak D [7]	3	1/1	2	0	1	0	1	0	0	0	0
1993	Chen KT [13]	3	1/1	2	1	0	NA	NA	0	1	0	0
1994	Van Vuuren PA [14]	3	NA	1	2	0	0	NA	0	1	0	0
1995	Tew S [15]	4	NA	0	4	0	NA	NA	0	4	NA	NA
1997	Heshmati HM [5]	12	1/1	3	9	NA	3	3	0	3	0	0
1998	O'Connell M [16]	7	NA	4	2	1	2	1	0	3	1	0
1998	Kennedy TL [6]	3	2/2	1	1	1	1	1	0	1	NA	NA
2000	Tradati N [17]	4	NA	2	2	0	0	1	0	1	0	0
2001	Moncet D [18]	3	NA	0	3	0	2		0	3	0	0
2001	Doshi SV [19]	14	3/5	5	6	3	5	3	0	10	3	0
2002	Cignarelli M [20]	3	0/1	0	0	3	0	1	0	NA	0	0
2002	Patel SG [4]	5	NA	4	1	0	0		0	0	1	0
2004	Miccoli P [21]	18	10/10	1	17	NA	6	3	0	18	2	0
2004	Luna-Ortiz K [22]	5	2/3	2	2	1	1	0	0	3	1	1
2006	Falvo L [23]	4	1/1	1	2	1	1	1	0	1	1	0
2006	Plaza CP [10]	5	1/4	1	3	1	1	1	0	5	0	0
2009	Hartl DM [9]	18	3/4	2	0	16	9	12	0	12	0	0
2011	Forest VI [8]	9	1/1	1	6	2	4	2	0	8	2	0
2011	Wang Y [24]	3	1/2	0	0	3	0	2	0	NA	0	0
2012	Dzodic R [1]	12	0/1	0	1	11	3	6	0	5	2	0
2012	Choi YM	10	9/10	4	3	3	2	2	1	6	2	1
Total	23	163	36/48	44	67	52	43	36	1	90	16	2
Available data		163	48	163	163	163	119	52	163	157	156	156
%			75	27	41	32	36	69	0.6	57	10	1.2

FNAB, fine-needle aspiration biopsy; SO, Sistrunk operation; SO/TT, Sistrunk operation with total thyroidectomy; LN, lymph node; RAI, radioactive iodine; NA, not available.

sion with palpable neck lymph nodes [2]. However, it is usually indistinguishable from a benign TGDC. The diagnosis is frequently made post-operatively by histopathological examination of the resected tissues [1].

There are some features of TGDC carcinoma that are revealed by ultrasonography or CT. The finding of a mural mass, especially with micro-calcifications, on a ultrasonography examination is strongly suggestive for carcinoma in the cyst [20]. In CT, carcinomas have either a dense or enhancing mural nodule, calcification within the cyst, or both [25]. These non-invasive imaging modalities also help to assess the thyroid gland and the neck.

FNAB is a relatively simple procedure and is a valuable test for pre-operative planning or counselling. Chen *et al.* [13] stated that FNAB is the most reliable

method of detecting a malignant process in midline neck masses before surgical intervention. Others have insisted that FNAB should be considered in all patients except children [4, 5, 22]. However, routine FNAB of all TGDCs, especially in children, may not be cost-effective because of the low frequency of carcinoma [5]. Further, the diagnostic accuracy of FNAB is not high. Sensitivity rates of 56% to 62% and a positive predictive value of 69% have been reported [26, 27]. The false-negative diagnosis by FNAB is mostly due to hypocellularity that results from dilution from the cystic contents [28]. The ultrasonography assistance during FNAB may enhance precision of cytological sampling if mural masses are present in the cyst, and thus may significantly reduce the false-negative diagnostic rate [9, 20]. In our series, FNAB was performed in all

patients. Among them, four patients underwent ultrasonography-guided FNAB. There was only one false-negative result when manual FNAB was used. A negative FNAB result should not rule out a diagnosis of TGDC carcinoma if the clinical suspicion is high [8].

Papillary adenocarcinoma comprised 75% to 85% of the tumors reported in the literature with mixed papillary/follicular the next most common (7%). Squamous cell carcinoma constituted approximately 5% and tended to have the worst prognosis. Medullary carcinoma has never been reported in a TGDC, which can be explained by the embryologic derivation [4, 6, 8]. Papillary carcinoma was also the most common pathologic type of cancer in our series. In fact, no other pathologic types were encountered. Two theories have been proposed to explain the origin of TGDC carcinoma. The first theory is that the carcinoma arises *de novo* from the cyst. This is supported by the fact that thyroid follicles are known to exist in a TGDC and could potentially undergo malignant transformation. The second theory proposes that the carcinoma is a metastasis from an occult primary tumor in the thyroid gland [3, 8].

The prognosis associated with TGDC papillary carcinoma is excellent [3, 5]. In a review by Patel *et al.* [4], with a median follow-up of 71 months, the 5- and 10-year Kaplan-Meier overall survival was 100% and 95.6%, respectively. The univariate analysis revealed that the only significant predictor of overall survival among patients with TGDC carcinoma was the extent of surgery for the cancer [4]. Patients treated with simple excision of the cyst fared significantly worse than those who had SO with 10-year overall survival rates of 75% and 100%, respectively. The effect of finding microscopic foci of well-differentiated thyroid carcinoma in an otherwise normal thyroid gland has been debated extensively [10].

Multicentricity of PTC in the thyroid gland is common in up to 33-40% of cases [2, 7]. However, the true incidence could be underestimated because not all patients get a total thyroidectomy along with excision of the TGDC. Cervical lymph node metastasis from papillary carcinoma of a TGDC has been reported in 7-25% of cases, and distant metastasis have been described in 1.3% of cases [2, 4, 8, 22].

Recently, the concept of stratification by risk has been suggested. Plaza *et al.* [10] recommended more aggressive treatment including total thyroidectomy and RAI therapy for patients deemed to be at high risk.

They defined high risk characteristics as being older than 45 years, having a history of radiation exposure, a tumor in the thyroid on radiological evaluation, having clinical or radiological nodes, a tumor more than 1.5cm in diameter, cyst wall invasion, or positive margins on histopathologic examination [10]. We examined this recommendation for 56 subsequent cases, including the cases at the Asan Medical Center. There were 47 cases that underwent SO/TT. Among 31 patients with risk factors, 19 patients (61.3%) showed PTC in the thyroid. Among 16 patients without risk factors, 8 patients (50%) showed PTC in thyroid. ($p=0.54$) This result is not statistically significant and is not sufficient to support Plaza's suggestion. Additional measures are necessary to determine the extent of surgery.

Dzodic *et al.* [1] found that the extent of lymph node dissection is also a factor in the prognosis of the disease. They stated that for TGDC carcinoma surgery, SO/TT with level I dissection is mandatory. They further stated that level II-IV dissection should be performed depending on the pathology of biopsied level II/III nodes. Level VI dissection was also recommended when carcinoma lesions are detected in the thyroid.

Long-term follow-up is mandatory regardless of whether the patient underwent a total thyroidectomy [8, 19]. Delayed metachronous PTCs in the thyroid gland, several years after a SO, have been reported [21]. In patients treated with SO, no data are available to clearly support the role of thyroid suppression. Nevertheless, most experts share the opinion that under these circumstances, the suppression of one possible stimulus to the thyroid tissue could be accomplished by keeping the thyroid-stimulating hormone between 0.1 and 0.5 mIU/L [10].

In conclusion, when TGDC carcinoma is suspected pre-operatively, meticulous high-resolution ultrasonography of the thyroid and neck should be performed. When features suggestive of TGDC carcinoma (*e.g.* a mural mass, especially with micro-calcifications) are found, ultrasonography-guided FNAB is recommended. If there are suspicious lesions in the thyroid or lymph node, SO/TT and lymph node dissection should be performed.

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