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Pathological evaluation of differentiated thyroid cancer in patients with positive serum thyroglobulin and negative iodine scan

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Abstract. – OBJECTIVE: There is no investigation that emphasizes the pathology of DTC (differentiated thyroid cancer) patients with positive Tg and negative iodine scan. The present study was performed to assess the pathology of these patients.

MATERIALS AND METHODS: In this retrospective study, the records of 500 patients with differentiated thyroid cancer between June 2005 and November 2011 were assessed, and those patients who had elevated serum thyroglobulin (Tg) with a negative whole body I-131 scan (Tg+/WBS-) were included in the study. Patients were followed for clinical and pathological findings of thyroid cancer, including type, variant, local invasion and cervical lymph node metastasis, and serum Tg, TgAb, and TSH levels.

RESULTS: A total of 38 patients, including 31 (81.6%) females and 7 (18.4) males with a mean age of 44.2 ± 15.6 years (range, 14 to 77 yrs) took part in the study. All 38 patients had the papillary type of differentiated thyroid cancer (PCDTC), and none had the follicular type of differentiated thyroid cancer (FCDTC). For the variant type of PTC in 16 patients, it was found that 7 were classic type (43.8%), 7 were follicular type (43.8%), and 2 were tall cell (12.4%) for papillary thyroid cancer. In 22 patients no distinct variant had been reported.

CONCLUSIONS: This report demonstrated that all of the 38 patients were PTC (100%), which is different from other previous studies. It may be concluded that the overall pathologic subtypes changes of DTC could mainly be due to the iodine fortification program in various geographic regions. The relationship between DTC pathologic subtypes and frequency of Tg+/WBS- condition was difficult to assess in this work. Therefore, further studies are required to evaluate this issue.

Key Words:
Differentiated thyroid cancer (DTC), Pathologic subtype, Papillary thyroid cancer (PTC), Follicular thyroid cancer (FTC), Positive thyroglobulin and negative iodine scan. (Tg+/WBS-).

Abbreviations

DTC, differentiated thyroid cancer; PTC, papillary thyroid cancer; FTC, follicular thyroid cancer; Tg+/WBS-, positive thyroglobulin and negative iodine scan; WHO: World Health Organization; UNICEF, United Nations Children's Fund; ICCIDD, International Council for the Control of Iodine Deficiency Disorders; TSH, Thyroid stimulating hormone.

Introduction

Differentiated thyroid carcinoma (DTC) is usually considered by an indolent course with low morbidity and mortality[1]. The main treatment of DTC includes total or near total thyroidectomy, together with radioiodine ablation[2]. Likewise, follow-up is carried out with ^{131}I whole body scan (^{131}I WBS) and serum thyroglobulin (Tg) measurement[3]. There is a good association between the presence of thyroid tissue and serum-stimulated thyroglobulin (Tg) levels[4,5]. Conversely, discordant results between ^{131}I WBS and Tg have been found in 15-20% of patients, who show high serum Tg but negative ^{131}I WBS[6-8].

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The reason is not clearly understood, but there are several theories to explain it e.g. micrometastases with lesion size below the resolution power of the diagnostic equipment[9-12], a dissociation between Tg synthesis and the iodine-trapping mechanism[10], micrometastases which do not accumulate sufficient iodine to be detected by low radioiodine activity[13], loss of the capacity to express the sodium/iodine symporter[13], and a recent study with contrast agents or using foods with high iodine levels[14].

In addition, based on another theory, an alternative hypothesis attributes high levels of serum Tg to illegitimate transcription of mRNA for Tg in non-thyroidal cells or ectopic thyroid tissue (e.g. intrathymus)[9].

Several reviews have argued this clinical dilemma, and some experts recommend therapy with high doses of ^{131}I to eradicate the metastatic lesions[15]. In contrast, other reports have demonstrated a lack of the efficacy of radioiodine therapy in these subgroups[11,16,17]. Thus, radioiodine therapy has been suggested for therapeutic management, but with mixed results[18,19].

To date, many studies have been performed on different aspects of this condition, but there is no report that emphasizes the pathology of these DTC patients. The present work aimed to evaluate the pathology of these patients.

Materials and Methods

Participants and Study Design

This study recruited 500 patients who had a history of DTC over a period of seven years, from June 2005 to November 2011. Patients were followed for clinical and pathological findings of thyroid cancer, including type (papillary or follicular)[20], variant (classic, follicular, and tall cell for papillary thyroid cancer, etc.)[20], local invasion (extrathyroidal extension, vascular, or capsular invasion), and cervical lymph node metastasis and serum Tg, TgAb, and TSH levels.

Patients who had a serum Tg level more than 2 ng/ml, and thyroglobulin autoantibody (TgAb) less than 100 IU/ml with a negative diagnostic or subsequent post-ablation whole body ^{131}I scan (Tg+/WBS-) were included. A negative whole body ^{131}I scan was defined as the absence of remnants of thyroid tissue, regional, or distant metastasis. We excluded patients with insufficient data; as such, 38 patients satisfied the eligibility criteria, made available informed consent, and took part in the study. In addition, ^{131}IWBS and Tg levels were determined after stopping a month of levothyroxine and two weeks of liothyronine. Serial monitoring was performed using serum Tg and TgAb measurements, and ^{131}IWBS. At the time of the diagnostic ^{131}IWBS, all cases had serum TSH levels above 30 mIU/l. Also, post-therapy scanning was scheduled to be undertaken just before the patient was released after ^{131}I therapy. This research complies with the Declaration of Helsinki, and endorsed by the institutional Ethics Committee of Shahid Beheshti University of Medical Sciences.

Acquisition Protocols

For ^{131}I scintigraphy, the patients orally received 185 MBq (185 MBq) ^{131}I, and scanning was performed 48 h later. Planar and single photon emission computed tomography (SPECT) images were acquired by a double-head gamma camera (ADAC Genesys, Milpitas, CA, USA) with a high-energy, parallel hole collimator, where the energy setting was at 364 keV ± 10%. The images were interpretated by two experienced nuclear medicine physicians.

Measurement of Serum Thyroglobulin

Serum thyroglobulin (Tg) and anti-Tg antibody levels were measured by radioimmunoassay, using commercial kits [BRAHMS Tg-plus DYNO test and BRAHMS anti-Tgn DYNO test (Diagnostica, Hennigsdorf, Germany)]. As TSH (RADIM, Italy) was elevated in all patients, Tg levels ≥ 2 μg/L was considerated abnormal[21]. Since circulating AbTg interferes with Tg assays, we routinely screened all patients for serum anti-Tg antibody using passive hemagglutination. Patients with elevated anti-Tg antibody and negative Tg were omitted from this study. In addition, serum TSH was determined with a third-generation double antibody assay.

Statistical Analysis

Continuous variables are expressed as mean ± SD, and categorical variables as the absolute values and percentages. For normally distributed data mean ± SD was used, otherwise median was reported.

Results

A total of 38 patients, including 31 (81.6%) females and 7 (18.4%) males with a mean age of 44.2 ± 15.6 years (range, 14 to 77 years) participated in the research. The mean age at diagnosis of patients was 39.4 ± 16.5 year (range, 13 to 76) years.

The mean interval between diagnosis (thyroidectomy) and ablation with I-131 were 6 ± 10.3 months (range, 1 to 55 months). In only one patient this interval was 55 months, but in remaining patients were less than 24 months.

The mean serum Tg level was 96.9 ± 140.5 ng/ml (range, 2.3 to 729 ng/ml).

The mean number of ablation with ^{131}I was 3.2 ± 2.4 (range, 1 to 15). In only one patient the number of ablations with ^{131}I was 15, but in remaining patients were less than 7.

The mean cumulative doses of ^{131}I dose were 9.6422 ± 15.762 GBq (260.6 ± 426 mCi), ranging from 3.7 to 55.5 GBq (100 to 1500 mCi). In only one patient, the cumulative I-131 dose was 5.55 GBq, but in remaining patients were less than 37 GBq.

All 38 patients had the papillary type of differentiated thyroid cancer (PCDTC), and none had the follicular type of differentiated thyroid cancer (FCDTC). For the variant type of PTC in 16 patients, it was found that 7 were classic type (43.8%), 7 were follicular type (43.8%), and 2 were tall cell (12.4%) for papillary thyroid cancer. In 22 patients, no significant variant was reported.

In 16 patients, the mean size of the largest tumor diameter was 2.9 ± 1.5 cm (range, 1 to 5.5 cm), and in 22 patients no significant tumor size was reported.

In this study, 24 (63.2%) had no local invasion, and 10 (26.3%) had local invasion to surrounding soft tissue including 6 (15.8%) extrathyroidal extension, 3 (7.9%) vascular, and 1 (2.6%) capsular invasion. Status of local invasion was unknown in 4 (10.5%).

Cervical lymph node metastasis was positive in 17 (44.7%) patients, negative in 18 (47.4%), and not reported in 3 (6.9%).

Discussion

In our series of 500 patients with differentiated thyroid cancer who were admitted for ablation with ^{131}I, 38 patients (7.6%) had high serum Tg level but negative ^{131}IWBS.

An important point of this study is that all of the 38 (100%) patients were PTC (100%). In our previous work in another center, 20 out of 21 (95.2%) patients had the papillary type of differentiated thyroid cancer (PCDTC), and the remaining 1 case had the follicular type of differentiated thyroid cancer (FCDTC)[2].

In a number of researches of Tg+/WBS- patients, the histologic subtypes of DTC patients were mentioned[22]. Ong et al[20] showed 15 (88.2%) cases of PTC, 1 case of FTC, and 1 case of Hürthle cell cancer out of 17 DTC patients in 2005 in Singapore. Fatourechi et al[15] demonstrated 18 (75%) cases of PTC, 5 cases of FTC, and 1 case of Hürthle cell cancer out of 24 DTC patients in 2002 in Minnesota. Muros et al[21] showed 8 (80%) cases of PTC, and 2 cases of FTC out of 10 DTC patients in 2000 in Spain.

In a study of 56 Tg+/WBS- patients, 32 were reported as PTC (57%), 14 as FTC, and 10 with Hürthle cell carcinoma[23]. Pacini et al[15] observed 70 cases of PTC with Tg+/WBS- in 2001 in Italy (100%). Pachucki et al[24] reported 20 cases of PTC and 1 case of FTC in Pennsylvania in 1997 (95.2%). Kabasakal et al[25] referred 18 cases of PTC (66.6%), 3 cases of FTC, 4 cases of Hürthle cell cancer, and 2 cases of tall cell cancer in Turkey in 2004.

The relationship between DTC pathologic subtypes and percentage of Tg+/WBS- condition was difficult to assess in this paper; however, it may be concluded that the overall pathologic subtypes changes of DTC could mainly be due to the iodine fortification program in various geographic regions. WHO/UNICEF/ICCIDD[26] recommended universal salt iodization as the main strategy to eradicate iodine deficiency disorders, and subsequent programs were carried out worldwide in 1990[27]. These programs contributed to the elimination of iodine deficiency in many countries, including Iran[28]. This result most likely accounts for the diminished FTC and increased PTC appearances in our country.

In this case, there are few investigations that assessed DTC subtype changes in the pre- and post-completion of the WHO program for the universal elimination of iodine deficiency.

Elise et al[29] studied clinical and pathological features and prognostic factors in 4187 DTC patients, subdivided into two groups – group 1 (n=1215) and group 2 (n=2972) – diagnosed before and after 1990, respectively. They showed a PTC diagnosis accounted for the majority of patients in both groups. However, a significant reduction of FTC (from 19.5% in group 1 to 9.0% in group 2) was observed.

Woodruff et al[30] compared DTC subtypes in an iodine-deficient country with those in a developed country. At the African centers, 322 patients underwent thyroidectomy for cancer from 1980 to 2004. In total, 31.5% had PTC, and 30.3% had FTC. From 1980 to 1989, 27.3% had PTC and 35.8%

had FTC. From 1990 to 2004, 35.7% had PTC and 24.8% had FTC. At the American centers, 105 patients underwent surgery for thyroid cancer from 1997 to 2008; 79% had PTC and 7.6% had FTC. They concluded that FTC is still common in developing countries, whereas PTC is the main subtype in developed countries, and attempts to reduce iodine deficiency may result in better outcomes by changing to a less aggressive subtype[30].

Conclusions

This article demonstrated that all of the 38 patients were PTC (100%), which is different from other previous studies. It may be concluded that the overall pathologic subtypes changes of DTC could mainly be due to the iodine fortification program in various geographic regions. The relationship between DTC pathologic subtypes and incidence of Tg+/WBS- condition were difficult to assess in this study. Therefore, further studies are required to evaluate this issue.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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