Distant and Lymph Node Metastases of Thyroid Nodules with No Pathological Evidence of Malignancy: A Limitation of Pathological Examination

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Abstract. Among thyroid nodules arising from follicular cells, benign nodular goiter is thought not to metastasize to regional or distant organs. However, we encountered five cases that were pathologically diagnosed as benign nodular goiter but showed metastasis. The prevalence of benign nodular goiter showing metastasis was 0.17% (5 of 2978 patients). On pathology, there were no detectable signs of carcinoma or follicular adenoma lesions. Two patients showed lymph node metastasis that was pathologically confirmed as metastasis of nodular goiter. One was preoperatively and another was postoperatively detected by ultrasonography. These patients also showed distant metastases that could be ablated by radioiodine. One patient preoperatively showed lung metastasis and the remaining two showed lung and bone metastases and bone metastasis postoperatively. Pathological diagnosis of thyroid nodules has limitations, and cases diagnosed as benign nodular goiter should still undergo careful follow-up.

Key words: Nodular goiter, Thyroid, Benign, Metastasis

THYROID nodules arising from follicular cells are classified broadly into two categories, carcinoma and benign nodule. Carcinoma is classified into papillary, follicular and anaplastic carcinomas and benign nodule typically includes follicular adenoma and nodular goiter. It is often difficult to differentiate follicular carcinoma and adenoma and careful pathological examination is needed to determine whether capsular and/or vascular invasion is present. If these invasions are overlooked because they are too minimal, postoperative metastasis might be observed in cases that were previously diagnosed as “follicular adenoma”. Except for anaplastic carcinoma, thyroid carcinomas usually have mild characteristics and show a good prognosis. However, since these lesions can show recurrence to regional lymph nodes and distant organs such as the lung and bone, careful postoperative follow-up is required [1, 2].

Usually postoperative follow-up is less carefully performed for benign nodules, because benign nodules are thought not to metastasize to regional and distant organs. However, of the patients who underwent surgical treatment in our department between 1990 and 2005 and were pathologically diagnosed as having benign nodular goiter, there were five who showed metastasis to regional lymph nodes or distant organs. In this study, we reviewed these cases and considered how we should deal with this event.
Patients and Methods

Patients

Between 1990 and 2005, 4760 patients underwent surgery and were diagnosed by pathological examination as having benign nodular goiter. Of these, 1675 and 107 patients were associated with thyroid carcinoma and follicular adenoma, respectively, indicating that 2978 patients had benign nodular goiter only. To date, 5 (0.17%) of these patients were confirmed as having lymph node and/or distant metastasis after or before surgery, and were enrolled in this study. These consisted of 4 females and 1 male and patient ages ranged from 25 to 59 years. Metastasis was detected during postoperative follow-up in 3 patients, and before surgery in the remaining two.

Pathological examination

The histology of primary lesions of these five patients was reviewed by a coauthor (M.H.), and all were confirmed as benign nodular goiter with no malignant components or foci of follicular adenoma, because typical microscopic patterns such as a varied pattern consisting of various-sized follicles and the lack of complete encapsulation and nuclear features indicating papillary carcinoma were demonstrated [3].

Results

To date, five (0.17%) of 2978 patients who were diagnosed as having nodular goiter on pathological examination showed lymph node or distant metastases before or after surgery. Table 1 summarizes the profiles of these patients.

Patient 1

A 49-year-old woman had multiple nodules in both lobes of the thyroid, which were diagnosed as benign nodules on ultrasonography and fine needle aspiration biopsy (FNAB). However, lymphadenopathy in the central and lateral compartments was also detected on ultrasonography. On FNAB specimens from the lymph nodes, thyroid follicular cells were detected and we suspected that she had an occult thyroid carcinoma with lymph node metastasis. Therefore, total thyroidectomy with modified radical neck dissection was performed. Fig. 1-a and 1-b showed hematoxylin & eosin (H & E) staining of primary tumor and lymph node. The primary lesion in the thyroid was diagnosed as benign nodular goiter and there were no other malignant lesions in the thyroid on postoperative pathological examination. In the lymph nodes, follicular cells composing large follicles showing the same morphology as the primary goiter were detected. Furthermore, brain metastasis was detected by iodine scintigraphy of 3mCi that was performed one month after surgery (Fig. 1-c, d). This metastasis was ablated by radioiodine therapy. To date, this patient has remained alive for 209 months after the initial surgery and her serum thyroglobulin level remains undetectable.

Patient 2

A 58-year-old woman underwent lobectomy as the initial surgery for nodules of the thyroid, which were diagnosed as nodular goiter on pathological examination.

Table 1. Profiles of 5 patients with “benign nodular goiter” showing metastasis

<table>
<thead>
<tr>
<th>Case number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery/Gender</td>
<td>49/F</td>
<td>58/F</td>
<td>59/F</td>
<td>25/M</td>
<td>52/F</td>
</tr>
<tr>
<td>Tumor diameter (mm)</td>
<td>35</td>
<td>41</td>
<td>36</td>
<td>42</td>
<td>35</td>
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<tr>
<td>Preoperative Tg (ng/ml)</td>
<td>1027.3</td>
<td>51.6</td>
<td>433.5</td>
<td>8000&lt;</td>
<td>2579</td>
</tr>
<tr>
<td>Surgical design of initial operation</td>
<td>*TT+**M</td>
<td>Lobectomy</td>
<td>TT</td>
<td>***CT</td>
<td>TT</td>
</tr>
<tr>
<td>Period between detection of metastasis and surgery (months)</td>
<td>Before surgery</td>
<td>37</td>
<td>Before surgery</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Organs showing metastasis</td>
<td>Lymph node</td>
<td>Brain</td>
<td>Lymph node</td>
<td>Lung</td>
<td>Lung Bone</td>
</tr>
<tr>
<td>Therapies for metastasis</td>
<td>Isotope</td>
<td>Re-operation Isotope</td>
<td>Isotope</td>
<td>Isotope</td>
<td>Isotope</td>
</tr>
</tbody>
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* Total thyroidectomy, ** Modified radical neck dissection, *** Completion total thyroidectomy.
tion. However, 37 months after surgery, enlargement of lymph nodes in the lateral and central compartments was detected on ultrasonography, although there were no pathological lesions in the remnant thyroid. Her thyroglobulin level was within the normal range at that time. On FNAB cytology of the lymph node, follicular cells were detected and metastasis from thyroid carcinoma was highly suspected. Furthermore, on CT scan performed before the second surgery, lung metastasis was detected. Therefore, she underwent completion total thyroidectomy with modified radical neck dissection. On pathological examination, however, there was no malignant lesion in the remnant thyroid. In the lymph node, follicular cells composing the large follicles were detected. These cells did not show any nuclear findings typical for papillary carcinoma and follicles in the lymph nodes had the same morphology as those detected in primary lesions dissected during the initial surgery. After radioiodine therapy for ablation of the lung metastasis, the thyroglobulin level decreased to an undetectable level. She has currently survived for 105 months after surgery.

**Patient 3**

A 59-year-old woman demonstrated nodular goiter of the thyroid and multiple nodules in the lung (Fig. 2) on mass screening. She underwent biopsy for the
nodule of the lung and was diagnosed as having metastasis from thyroid malignancy based on positive thyroglobulin staining, although the histology could not be determined. Therefore, she underwent total thyroidectomy. Based on careful pathological examination of the whole thyroid, the goiter was diagnosed as a benign nodular goiter with no malignancy. After surgery, her thyroglobulin level was 14.7 ng/ml under TSH suppression. Subsequently, she underwent radioiodine ablation therapy, but there was no apparent iodine uptake in the lung and the patient has undergone TSH suppression therapy only. Although lung metastasis has slowly progressed and her thyroglobulin level is elevated to 328 ng/ml, she is currently alive with no symptoms.

**Patient 4**

A 25-year-old man underwent lobectomy as an initial surgery at the age of 19 and his pathological diagnosis was adenomatous nodule with no malignancy. Six years later, since the multiple nodules in the remnant thyroid enlarged, he underwent completion total thyroidectomy as a second surgery. Pathological diagnosis of the second surgical specimen was again benign nodular goiter with no malignant lesions. After the second surgery, his thyroglobulin level decreased from over 8000 ng/ml to 77 ng/ml, but gradually elevated again to 310 ng/ml 24 months later. Radioiodine scintigraphy was then performed 27 months after the second surgery, and metastases to the lung and skull were detected (Fig. 3) and confirmed by SPECT CT fusion image. He has undergone radioiodine ablation therapy one time and is scheduled to undergo a second such therapy session in the future.

**Patient 5**

A 52-year-old woman underwent total thyroidectomy for multinodular goiter. FNAB cytology from one of the nodules indicated follicular tumor (indeterminate). However, pathological diagnosis was benign nodular goiter with no evidence of follicular adenoma, follicular carcinoma or papillary carcinoma. Twenty-nine months after total thyroidectomy, her thyroglobulin level suddenly elevated from undetectable level to 59 ng/ml. Bone metastasis was detected by radioiodine scintigraphy and ablation therapy is currently being planned.

**Discussion**

Previously, some groups demonstrated benign metastasizing goiter, but all of these cases were published before the beginning of the 1970s [4–6] and no studies have been published since the level of pathological diagnosis has risen to the present standard.

In this study, we reviewed five cases of multinodular goiter showing lymph node or distant metastasis.
This event was observed in 0.17% of patients who were pathologically diagnosed as benign nodular goiter with no signs of carcinoma or follicular adenoma lesions. We previously reported a case of follicular neoplasm showing the growth of subcutaneous nodule by FNAB seeding [7]. Although it was diagnosed as follicular carcinoma based on FNAB seeding, there were no malignant findings in the thyroid on pathological examination of the total thyroidectomy specimen, thus the lesion would be diagnosed as nodular goiter unless such a finding is present. Similarly, in the lymph nodes of patients 1 and 2, metastases showing the same morphological structures as primary nodular goiters were observed as shown in Fig. 1. This indicates that these nodular goiters diagnosed as non-malignant actually showed a malignant behavior or in fact, were very well differentiated carcinomas, although there were no detectable pathological findings indicating malignancy. Indeed, there is a variant of papillary carcinoma, which is termed “macrofollicular variant” in the WHO classification [8]. This variant is composed predominantly or exclusively of macrofollicles and morphologically resembles benign nodular goiter. This variant is exceedingly rare and accounted for only 0.3% in our series [9], but may have been misdiagnosed as benign goiter in the past. Indeed, Albores-Saavedra et al. reported 17 cases of this variant and 6 cases were found on review of benign thyroid lesions [10]. They also reported that some of these lesions had nuclei that were less clear than those of conventional papillary carcinoma, which is the reason for misdiagnosis. If the nuclear findings are less clear or completely absent, the lesion can no longer be diagnosed as papillary carcinoma. However, this variant generally has an indolent character, although one case that recurred with anaplastic transformation was reported [11].

Cervical node metastasis was observed in 2 of 17 cases in the series reported by Albores-Saavedra et al. [10], but none of these patients showed distant metastasis, indicating the possibility that our 5 cases had an entity that differed from this variant. Another possibility that tiny papillary or follicular carcinoma that was undetectable on pathological examination metastasized to distant organs could also explain the distant metastasis in patients 3–5. We are not certain which is correct for these patients, because the pathological diagnoses of metastatic lesions were unclear or not examined.

It is beyond the limitation of pathological diagnosis to completely exclude this event. It is impossible to predict whether nodular goiter will metastasize to the lymph nodes and/or distant organs or to detect absolutely all microscopic thyroid malignancies on pathological examination. However, this study presented two key points for the early detection of metastasis. One is the serum thyroglobulin level. Radioiodine scintigram was performed for patients 4 and 5 because the thyroglobulin level was elevated even after total thyroidectomy. Lung metastasis was incidentally detected by mass screening for patient 3. However, her thyroglobulin level, which was 14 ng/ml after surgery, was not completely decreased and was gradually elevated to 328 ng/ml. Therefore, even if lung metastasis was not preoperatively detected, it would have been found by postoperative detection of an elevated thyroglobulin level. Occasional follow-up of the thyroglobulin level may contribute to early detection of metastasis from “benign nodular goiter”, although the cost of thyroglobulin measurement varies from country to country and for some countries, it may be difficult to perform routine thyroglobulin measurement.

Another useful tool is ultrasonography. Lymph node metastasis was preoperatively detected in patient 1, although there were no malignant findings in the thyroid. Furthermore, in patient 2, follow-up by ultrasonography detected lymph node metastasis. Therefore, in preoperative ultrasonographic examination for nodular goiter, screening for any abnormality in the lymph node is required. Furthermore, even after lobectomy for benign goiter, follow-up by ultrasonography, even if not frequent, may contribute to detecting this phenomenon in the early stage. All patients in our series showed distant metastasis, including the two having lymph node metastasis, which may be one of the characteristics of benign nodular goiter showing metastasis. Therefore, search for distant metastasis is also recommended after surgery by radioiodine scintigram or PET-scan if metastasizing goiter is suspected based on pathological examination or high thyroglobulin level.

In summary, we presented 5 patients diagnosed as having “benign nodular goiter” showing metastasis to regional or distant organs. Pathological diagnosis of thyroid nodules has limitations, and we continue to carefully follow patients diagnosed as having benign nodular goiter.
References


