“Nodule in Nodule” on Thyroid Ultrasonography: Possibility of Follicular Carcinoma Transformed from Benign Thyroid Tumor

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What Is Known about This Topic?

- To date, it has been very difficult to differentiate follicular carcinoma from follicular adenoma by ultrasonography. Tumors that show a “nodule in nodule” appearance on ultrasonography are diagnosed as follicular carcinoma or follicular neoplasm within benign tumors histopathologically. The ultrasonographic significance of this appearance has not been clarified.

What Does This Case Report Add?

- A small number of follicular carcinoma cases or follicular neoplasms may present with a “nodule in nodule” appearance on ultrasonography. It is suggested that a follicular carcinoma or neoplasm with this appearance has transformed from a benign lesion.

Keywords

Thyroid · Nodule in nodule · Diagnosis · Follicular carcinoma · Ultrasonography

Abstract

Background: It is generally considered impossible to differentiate follicular carcinomas from follicular adenomas by means of ultrasonography or cytology before surgery. Therefore, follicular carcinoma is histopathologically diagnosed by verifying capsular and/or vascular invasion after surgery. However, ultrasonography may play an important role in diagnosing follicular carcinoma preoperatively in a small number of cases. **Case Description:** Four cases of follicular carci-

noma or follicular neoplasm that transformed from a benign thyroid tumor and demonstrated a “nodule in nodule” appearance on ultrasonography are presented in this report. Characteristic ultrasound features of such patients are: (1) a “nodule in nodule” appearance, (2) a well-defined boundary line between the nodules, and (3) separate distribution of blood signals within each nodule. **Conclusion:** A small number of patients with follicular carcinomas or follicular neoplasms may present with a “nodule in nodule” appearance on ultrasonography. It was suggested a long time ago that follicular carcinomas may develop from benign thyroid tumors. The fact that follicular carcinomas appear within benign tumors may be evidence of thyroid tumorigenesis.

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Introduction

Follicular carcinoma is histopathologically diagnosed by verifying capsular and/or vascular invasion after surgery. Follicular carcinomas as well as follicular adenomas have some ultrasonic features. These include a predominantly solid, homogeneous internal echo, hypoechoic echogenicity, presence of halo, and central blood signals [1–4]. Therefore, it is generally considered impossible to differentiate follicular carcinomas from follicular adenomas by ultrasonography. However, some characteristic ultrasound features, such as tumor thrombus [5] and tumor protrusion [6], can provide useful information for

the preoperative diagnosis of follicular carcinoma in some patients who show “follicular neoplasm” on cytology. In this report, we present 4 patients with a follicular carcinoma or neoplasm who demonstrated a “nodule in nodule” appearance on ultrasonography, which was suggested to be a follicular carcinoma or neoplasm transformed from a benign lesion located in the outer nodule.

Case Series

Patient 1: A 49-Year-Old Woman

The serum study revealed: free T4 1.10 ng/dL (reference range 0.70–1.60), free T3 3.27 pg/mL (1.70–3.70), thyroglobulin 942.4

Fig. 1. Ultrasonography and histopathological appearance of the nodule of patient 1. **a** Color-Doppler ultrasonography. Tumor: “nodule in nodule” appearance. Inner nodule: solid and hypoechoic content, $26 \times 14 \times 19$ mm. Outer nodule: solid and isoechoic content, $31 \times 16 \times 22$ mm. The boundary line between the nodules is well defined, while blood signals have separate distributions. **b** B-mode ultrasonography. Tumor: “nodule in nodule” appearance. **c** Histopathological appearance of the thyroid nodule. HE stain. The nodule demonstrated a 2-layered structure, and was diagnosed as “follicular adenoma” as a whole at that time. **d** Histo-

pathological appearance of the lymph node. HE stain. Colloid-containing follicles consisted of tumor cells observed in the lymph node. It was diagnosed as a metastatic lymph node from follicular carcinoma. **e** MIB-1 staining of the same metastatic lymph node. Labeling index 5–10%. **f** Histopathological appearance of the inner tumor. HE stain. The microfollicular structure consisted of tumor cells and colloid. **g** MIB-1 staining of the inner tumor. Labeling index 5–10%. **h** Histopathological appearance of the outer tumor. Macrofollicular structure and colloid are observed. **i** MIB-1 staining of the outer tumor. Labeling index <1%.

ng/mL (<35), and TgAb <28.0 (<39.9). The nodule in the right lobe presented with a “nodule in nodule” appearance on ultrasonography (Fig. 1a, b). The nodule consisted of an inner nodule with hypoechoic content (26 × 14 × 19 mm) within an outer nodule with isoechoic content (31 × 16 × 22 mm). A boundary line between the outer and inner nodule was well defined. Blood signals existed within each nodule separately or individually on Doppler ultrasonography (Fig. 1a). Fine-needle aspiration cytology revealed a “follicular neoplasm.” A right lobectomy of the thyroid was performed, and the whole nodule was diagnosed as a follicular adenoma (Fig. 1c) at that time. The serum thyroglobulin level decreased to 22.8 ng/mL after surgery. She was followed up without medication. Eight years after the surgery, her serum thyroglobulin level had increased to 2,826.0 ng/mL. Ultrasound examination of the thyroid and neck revealed the remnant left lobe of the thyroid and a swollen lymph node (23 mm) in the right neck. Cytology revealed “follicular neoplasm” from the swollen

lymph node. Lymph node dissection of the right neck and left lobectomy of the thyroid were performed. Subsequently, whole-body scintigraphy using radioiodine (^{131}I : 150 mCi) revealed an abnormal uptake in the twelfth thoracic vertebra and second rib on the right. Histopathological examination revealed a metastatic lymph node (Fig. 1d) from the follicular carcinoma and no tumors in the left remnant lobe. The MIB-1 labeling index was 5–10% in the metastatic lymph node (Fig. 1e). The initial diagnosis of the tumor in the right lobe, which had been “follicular adenoma” 8 years before, needed to be reconsidered. Histopathological reexamination of the right lobe tumor revealed a “nodule in nodule” appearance. The MIB-1 labeling index was 5–10% in the inner tumor (Fig. 1g) and <1% in the outer tumor (Fig. 1i). The tumor was clinically and histopathologically diagnosed as a follicular carcinoma (Fig. 1f) for the inner tumor with lymph node and bone metastasis within a follicular adenoma (Fig. 1h) as the outer tumor.

Fig. 2. Ultrasonography, resected specimen, and histopathological appearance of the nodule of patient 2. **a** B-mode ultrasonography. Tumor: “nodule in nodule” appearance. Inner nodule: hypoechoic content, 38 × 24 × 31 mm. Outer nodule: isoechoic content, 45 × 26 × 35 mm. The boundary line between the nodules is well defined. **b** Power-Doppler ultrasonography. Blood signals have separate distributions. **c** Schema of thyroid ultrasound. Tumor:

“nodule in nodule” appearance. **d** Sectional view of resected thyroid specimen. “Nodule in nodule” configuration: inner nodule (i), outer nodule (ii), normal thyroid tissue (iii). **e** Histopathological appearance (HE staining): inner tumor (i), outer tumor (ii), capsule of inner tumor (X), capsular invasion (arrow). **f** MIB-1 staining. Labeling index of the inner tumor 5–10% (i), labeling index of the outer tumor <1% (ii).

Fig. 3. Ultrasonography, resected specimen, and histopathological appearance of the nodule of patient 3. **a** B-mode ultrasonography. Tumor: “nodule in nodule” appearance. Inner nodule: hypoechoic content, partly cystic lesion, $19 \times 15 \times 16$ mm. Outer nodule: solid and isoechoic content, $41 \times 25 \times 29$ mm. The boundary line between the nodules is well defined. **b** Schema of thyroid ultrasound. Tumor: “nodule in nodule” appearance. **c** Sectional view of a resected thyroid specimen: inner tumor (i), outer tumor (ii), normal

thyroid tissue (iii). **d** Histopathological appearance of the tumors (HE staining): inner tumor (i), outer tumor (ii), normal thyroid parenchyma (iii). **e** Histopathological appearance of the inner tumor. HE stain. Solid and microfollicular structure. **f** MIB-1 staining of the inner tumor. Labeling index 10–20%. **g** Histopathological appearance of the outer tumor. Macrofollicular structure and colloid. **h** MIB-1 staining of the outer tumor. Labeling index <1%.

Patient 2: A 57-Year-Old Woman

The nodule showed a “nodule in nodule” appearance (outer: $45 \times 26 \times 35$ mm, inner: $38 \times 24 \times 31$ mm), a well-defined boundary line, and separate distribution of blood signals on ultrasonography (Fig. 2a–c). The sectional view of resected thyroid specimen presented a “nodule in nodule” configuration (Fig. 2d). Histopathological examination showed a solid or microfollicular structure of the inner tumor (Fig. 2e, i), a thin capsule (Fig. 2e, X) consisting of connective tissue in an intermediate layer, and macrofollicular structure of the outer tumor (Fig. 2e, ii). Tumor tissue of the inner tumor demonstrated complete penetration of the capsule and invaded tumor tissue of the outer tumor, i.e. capsular invasion (Fig. 2e, arrow). The MIB-1 labeling index was 5–10% in the inner tumor (Fig. 2f, i) and <1% in the outer tumor (Fig. 2f, ii). The tumor was histopathologically diagnosed as a follicular carcinoma with capsular invasion for the inner tumor within a follicular adenoma as the outer tumor.

Patient 3: A 70-Year-Old Woman

The nodule showed a “nodule in nodule” appearance (outer: $41 \times 25 \times 29$ mm, inner: $19 \times 15 \times 16$ mm), a well-defined boundary line, and separate distribution of blood signals on ultrasonography (Fig. 3a, b). Cytology revealed a “follicular neoplasm” of the inner nodule and “benign tumor” of the outer nodule, respectively. The sectional view of the resected thyroid specimen revealed a “nodule in nodule” configuration (Fig. 3c). Histopathological examination (Fig. 3d) showed a 3-layered structure: solid or microfollicular structure of the inner tumor (Fig. 3d, i; e), a thin capsule consisting of connective tissue in an intermediate layer, a macrofollicular structure of the outer tumor (Fig. 3d, ii; g), and normal thyroid tissue (Fig. 3d, iii). Neither capsular invasion nor vascular invasion was observed within the inner tumor. The MIB-1 labeling index was 10–20% in the inner tumor (Fig. 3f) and <1% in the outer tumor (Fig. 3h). The inner tumor was histopathologically diagnosed as a follicular adenoma (or follicular neoplasm) within a follicular adenoma as the outer tumor.

Fig. 4. Ultrasonography, resected specimen, and histopathological appearance of the nodule of patient 4. **a** B-mode ultrasonography. Tumor: “nodule in nodule” appearance. Inner nodule: hypoechoic content, $42 \times 23 \times 22$ mm. Outer nodule: isoechoic content, $79 \times 32 \times 60$ mm. The boundary line between the nodules is well defined. **b** Power-Doppler ultrasonography. Blood signals: separate distribution. **c** Schema of thyroid ultrasound. Tumor: “nodule

in nodule” appearance. **d** Sectional view of the resected thyroid specimen: inner tumor (i), outer tumor (ii). **e** Histopathological appearance of the inner tumor. HE stain. The microfollicular structure consisted of tumor cells. **f** MIB-1 staining of the inner tumor. Labeling index 10%. **g** Histopathological appearance of the outer tumor. HE stain. A macrofollicular structure was observed. **h** MIB-1 staining of the outer tumor. Labeling index <1%.

Patient 4: A 37-Year-Old Woman

The nodule showed a “nodule in nodule” appearance (outer: $79 \times 32 \times 60$ mm, inner: $42 \times 23 \times 22$ mm), a well-defined boundary line, and separate distribution of blood signals on ultrasonography (Fig. 4a–c). Cytology revealed a “follicular neoplasm” of the inner nodule and “benign nodule” for the outer nodule, respectively. The sectional view of the resected thyroid specimen presented a “nodule in nodule” configuration (Fig. 4d). Histopathological examination showed a solid or trabecular structure of the inner tumor (Fig. 4e) and macrofollicular structure of the outer tumor (Fig. 4g). Neither capsular invasion nor vascular invasion was observed within the inner tumor. The MIB-1 labeling index was 10% in the inner tumor (Fig. 4f) and <1% in the outer tumor (Fig. 4h). The tumor was histopathologically diagnosed as a fol-

licular adenoma (or follicular neoplasm) for the inner tumor within a follicular adenoma as the outer tumor.

Table 1 shows the ultrasonography, cytology, histopathology, and diagnosis details of the 4 patients with a “nodule in nodule” appearance.

Discussion

Follicular carcinoma is histopathologically diagnosed by verifying capsular and/or vascular invasion after surgery. However, it is clinically desirable for follicular car-

Table 1. Ultrasonography, cytology, histopathology, and diagnosis of the 4 patients with a “nodule in nodule” appearance on thyroid ultrasonography

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	49	57	70	37
Gender	female	female	female	female
<i>Ultrasonography</i>				
1. Appearance	nodule in nodule	nodule in nodule	nodule in nodule	nodule in nodule
2. Size, mm ¹ ; structure; echogenicity				
(A) Inner nodule	26; solid; hypoechoic	38; solid; hypoechoic	19; solid; hypoechoic	42; solid; hypoechoic~isoechoic
(B) Outer nodule	31; solid; isoechoic	45; solid; isoechoic	41; solid; isoechoic	79; solid; isoechoic
3. Boundary echo	(+)	(+)	(+)	(+)
4. Blood signals	separate	separate	separate	separate
Cytology of inner nodule	follicular neoplasm	follicular neoplasm	follicular neoplasm	follicular neoplasm
<i>Histopathology</i>				
1. Structure; MIB-1 labeling index				
(A) Inner tumor	microfollicular; 5–10%	solid; 5–10%	solid; 10–20%	solid~trabecular; 10%
(B) Outer tumor	macrofollicular; <1%	macrofollicular; <1%	macrofollicular; <1%	macrofollicular; <1%
2. Fibrous capsule of inner tumor	(+)	(+)	(+)	(+)
3. Invasion of inner tumor	(–)	capsular invasion (+)	(–)	(–)
4. Invasion of outer tumor	(–)	(–)	(–)	(–)
5. Metastasis	lymph node (+), bones (+)	(–)	(–)	(–)
Diagnosis of inner tumor	follicular carcinoma	follicular carcinoma	follicular adenoma (follicular carcinoma?)	follicular adenoma (follicular carcinoma?)

hypoechoic, hypoechoic internal content; isoechoic, isoechoic internal content; separate, separate distribution of blood signals on Doppler ultrasonography; microfollicular, microfollicular structure; macrofollicular, macrofollicular structure; invasion, histopathological findings of capsular invasion or vascular invasion.

¹ Maximum length.

cinoma to be diagnosed before surgery. Most follicular carcinomas and follicular adenomas demonstrate solitary, well-defined, solid, homogeneous, and hypoechoic or isoechoic nodules with a hypoechoic capsular-like zone and no adenopathy on ultrasonography [1–4]. It is considered impossible to differentiate follicular carcinomas from follicular adenomas by ultrasonography. Cytology also provides very similar findings between the 2 diseases. It is diagnosed as “follicular neoplasm” without a judgment of malignancy or benignancy on cytology. On the contrary, we previously reported a few cases of follicular carcinoma with a tumor thrombus [5] and tumor protrusion with intensive blood signals extending from the main tumor [6] detected by preoperative ultrasonography in combination with cytological findings of “follicular neoplasm.” Therefore, ultrasonography can provide useful information on the preoperative diagnosis of follicular carcinoma in some patients. The MIB-1 or Ki-67 labeling index is generally regarded as a proliferative marker of tumor and normal tissues. Many researchers reported that the MIB-1 or Ki-67 labeling index of follicular carcinoma was higher than that of follicular ade-

noma [7–10]. It is generally thought that the labeling index is helpful and acts as subsidiary information when diagnosing follicular carcinoma, although it is not one of the histopathological criteria of follicular carcinoma.

It was suggested a long time ago that follicular carcinoma may develop from a benign thyroid tumor [11–13]. At present, it is widely recognized that some undifferentiated (anaplastic) carcinomas are derived from differentiated thyroid carcinomas according to another malignant transformation [14–16]. The progression model of thyroid benign tumors and malignancies has been proposed based on a genetic study of tumorigenesis [16]. Differentiated thyroid carcinomas may be derived from thyroid follicular cells or benign tumors according to malignant transformation [16]. In this situation it can be suggested that tumor cells of the preceding benign tumor in these patients transformed into the newly modified or transformed cells, and formed the new tumor within the preceding benign tumor. This is because the histopathological appearance and MIB-1 labeling index are different between the 2 tumors.

When these 4 inner tumors are strictly diagnosed using the histopathological criteria, the tumors of patients 1 and 2 can be verified as follicular carcinomas according to the evidence of metastasis or capsular invasion, and those of patients 3 and 4 to be follicular adenomas according to the lack of evidence of invasion. However, we suggest that those of patients 3 and 4 might be follicular carcinomas because of the “nodule in nodule” appearance, histopathological appearance, and high MIB-1 labeling index. It is necessary to observe these patients carefully after surgery.

In conclusion, the preoperative detection of a “nodule in nodule” appearance on ultrasonography has a clinically important significance in patients with cytological findings of “follicular neoplasm.”

Disclosure Statement

The authors have no conflicts of interest to disclose.

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