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Distinguishing mummified thyroid nodules from malignant thyroid nodules

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Abstract

Aim: To study the ultrasonographic (US) differences between "mummified" thyroid nodules and malignant thyroid nodules in order to achieve a more accurate imaging-based diagnosis and to avoid unnecessary biopsy. **Material and methods:** We retrospectively reviewed the US features of mummified thyroid nodules, as confirmed by fine-needle aspiration cytology (FNAC), in 193 cases. The US features included content, echo, shape, margin, microcalcification, suspicious lymph nodes and some characteristic features, including the cystic wall shrinkage sign, the concentric configuration or finger sign, calcification and halo. All of these features were classified and compared with those of 109 malignant lesions. The changes of these mummified nodules during the follow-up period were also examined. **Results:** The cystic wall shrinkage sign and the concentric configuration or finger sign were highly specific indicators of mummified thyroid nodules and could be used to distinguish mummified nodules from thyroid cancer with a specificity of 91.7% and 99.9%, respectively. A continuous decrease in the cyst size was observed during follow-up. **Conclusions:** Mummified thyroid nodules are characterized by the cystic wall shrinkage sign and the concentric configuration or finger sign on US and a continuous decrease in size during follow-up. These features may be useful for the differential imaging-based diagnosis of mummified versus malignant thyroid nodules.

Keywords: mummified thyroid nodule; ultrasonography; fine-needle aspiration cytology

Introduction

The incidence of thyroid nodules in Western countries has been reported to be as high as 70% [1] and ultrasound (US) is the most commonly used imaging method for diagnosing thyroid nodules. Benign nodules, including nodular goiter and follicular adenoma, show clear boundaries and regular shapes on two-dimensional US imaging [2]. In contrast, malignant nodules feature a solid appearance, hypoechogenicity or even strong hypoechogenicity, an irregular shape, ill-defined margins, a taller-than-wide shape, microcalcification and extrathyroidal invasion. The reported sensitivity of US for the diagnosis of thyroid nodules ranges from 10–74% and specificity from 40–96% [3-5].

However, there is one benign nodule type that appears to be extremely similar to malignant nodules on two-dimensional US but only yields a brown material on fine-needle aspiration (FNA) and contains insufficient cell numbers for definite cytological examination. This causes confusion in determining the optimal surgical strategy. In some cases, patients undergo repeated FNA cytology (FNAC) or even surgery. On follow-up, these nodules appear to shrink from a large size to a small size. These lesions were first called mummified thyroid nodules by Lacout et al [6], and this type of thyroid nodule

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accounts for approximately 5–10% of all thyroid nodules evaluated by FNAC. Lacout et al [6] showed that regular eggshell calcifications, peripheral hyperechoic or hypoechoic rim, posterior shadowing, absence of intranodular vascularization, absence of ipsilateral suspicious lymph nodes, shrinkage and FNAC and US follow-up would contribute to establishing the final diagnosis of these benign nodules. In this retrospective study, the features of mummified thyroid nodules on US were analyzed with the goal of determining their characteristic features in order to achieve a more accurate imaging-based diagnosis and avoid unnecessary biopsy.

Materials and methods

Patients

A total of 4,050 thyroid nodules with FNAC results examined in our hospital from January 2016 to January 2018 were screened, and 193 cases with a definite diagnosis of mummified nodules were selected. The diagnostic criteria for mummified nodules were as follows [6,7]: 1) aspiration resulted in a brown, viscous sample; 2) features consistent with necrosis or repair (e.g., hemosiderin, multinuclear macrophages, and fibroblasts) observed on pathological analysis; and 3) normal follicular epithelial cells may or not be present while abnormal follicular cells and tumor cells were absent. The control group consisted of 109 thyroid malignant nodules, which were identified from among 254 thyroid nodules with FNAC results between January 1, 2018 and January 30, 2018. The inclusion criteria were as follows: 1) complete imaging data; and 2) cytological confirmation that the lesion was malignant according to the Bethesda system for reporting thyroid cytopathology (TBSRTC) [8].

US equipment and reagents

US was performed using Elite (Philips, The Netherlands), Hi Vision Ascendus (Hitachi, Japan), and DC-8 EXP (Mairui Corporation, China) devices. The frequency used ranged from 9–12 MHz.

Under supine cervical extension, imaging data, including size, echogenicity, margin, calcification and suspicion lymph nodules, were recorded and entered the database.

All US images from database were carefully observed by two physicians from the US department of our hospital, both with more than 10 years of experience. One physician observed and analyzed the differences between the two groups and proposed several characteristic features, including the cystic wall shrinkage sign, the concentric configuration or finger sign, calcification and halo. Nodules were classified by another physician who was blinded to the clinical and histopathological results according to guidelines provided by the American Thyroid Association (ATA) for adult thyroid nodules and differentiated thyroid cancer (2015) [3] and the Thyroid Imaging Reporting and Data System (TI-RADS) classification [9]. The latter physician also analyzed the features proposed by the first physician.

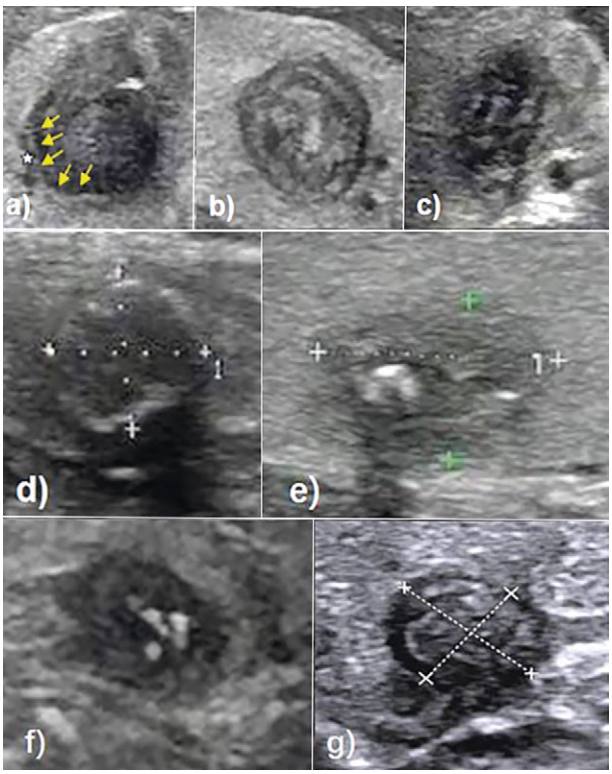

Fig 1. Characteristics of several types of mummified nodules: a) the cystic wall collapse sign: slightly wavy (arrows) crack-like hypoechoic signals visible between the nodule and thyroid parenchyma (stars); b) the concentric sign: hyperechoic and hypoechoic signals staggered around the center; c) the finger sign: staggered streaks of hyper- and hypoechoic signals; d) eggshell calcification; e) massive calcification; f) microcalcification; g) the halo sign.

The cystic wall shrinkage sign refers to a hyperechoic halo at the edge of the nodule that is slightly wavy or flat and usually incomplete. A fissure-like hypoechogenicity between the nodule and the thyroid parenchyma could be observed (fig 1a). The concentric configuration sign refers to the hypoechoic and hyperechoic parts of the nodule being centered within the nodule (fig 1b) and the finger sign refers to the hypoechoic and hyperechoic signals being staggered in a stripe pattern (fig 1c). In addition, we observed the following features: calcification, classified as eggshell calcification (fig 1d), i.e., an intact ring of strong signals around the nodule, massive calcification (fig 1e), or microcalcification (fig 1f). Halo denotes the presence of a hypoechoic ring around the nodule (fig 1g).

Because of the deficiency of intranodular blood in most malignant thyroid nodules, no observations of vascular flow were made in this study.

Table I. Demographic data, location and diameters of thyroid nodules

	Malignant nodules (n=109)	Mummified nodules (n=193)	p value
Age (years)	46.2±11.5	55.2±10.1	<0.01
Sex (m/f)	23/86	46/147	0.669
Nodule location (left/right)	45/64	102/91	0.056
Diameter (cm)	1.12±0.23	1.32±0.31	0.204

Table II. Conventional ultrasound information regarding thyroid nodules in the two studied groups

	Mummified nodules (n=193)	Malignant nodules (n=109)	p value
US features			
solid	193	101	<0.01*
hypoechogenicity	193	107	0.130*
Ill-defined margin	185	96	0.017
taller-than-wide shape	5	23	<0.01
microcalcifications	29	34	<0.01
suspicious lymph nodes	2	21	<0.01*
TI-RADS			
2	0	0	-
3	0	0	-
4			
4a	13	12	0.200
4b	135	54	<0.01
4c	26	34	<0.01
5	19	9	0.648
ATA			
high suspicion	185	94	0.02
intermediate suspition	8	13	0.011
low suspition	0	2	0.130*
very low suspition	0	0	-
benign	0	0	-

* Fisher's exact test; TI-RADS, Thyroid Imaging Reporting and Data System; ATA, American Thyroid Association.

FNAC procedure

All biopsies were performed by a physician with more than 5 years of experience in interventional US. The patient was maintained in the supine position with the neck extended. The skin overlaying the nodule was sterilized with povidone-iodine solution (LIRCON, Shandong, China) and 2% lidocaine (Beijing Yimin Pharmaceutical Company, Beijing, China) was applied as a local anesthetic. Two FNA samples were taken from each nodule using a 25-G needle (BD Biosciences, NJ, USA). The needle was inserted into the nodule with no vacuum aspiration and then moved back and forth for 5–10 passes. The collected material was directly smeared on a glass slide and immediately fixed in 95% ethyl alcohol (Beijing Zhenyuminsheng Pharmaceutical Company, Beijing, China). Hematoxylin-eosin staining was applied for the cytopathological diagnosis. To monitor potential complications, the patients remained under observation for an additional 30 minutes.

The study was approved by the Ethics committee and Institutional Review Board of Beijing Friendship Hospital (approval number 2018-P2-108-01).

Statistical analysis

All statistical analyses were performed using SPSS version 20.0 (SPSS, Inc., IL, USA). The chi-square test was used for the comparison of count data and the independent sample t-test was used for the comparison of measurement data. $p<0.01$ was considered statistically significant.

Results

All of the malignant thyroid nodules were papillary carcinoma. In table I and II the demographic data of the patients and the US findings in the mummified and malignant nodules are detailed. All mummified nodules were solid and hypoechoic were scored as 4 and classified as suspicious of malignancy.

US imaging features of mummified thyroid nodules

A comparative analysis revealed that the cystic wall shrinkage sign and the concentric configuration or fin-

Table III. Comparison between ultrasound findings of malignant and mummified nodules

	Malignant nodules (n=109)	Mummified nodules (n=193)	p value	Se (%)	Sp (%)
Cystic wall shrinkage sign	9 (8.3)	118 (61.1)	<0.01	61.1	91.7
Concentric or finger sign	1 (0.1)	17 (8.8)	<0.01*	8.8	99.1
Calcification					
Micro-	34 (31.2)	29 (15.0)	<0.01		
Massive	11 (10.9)	45 (23.3)	0.05		
Eggshell	0	6 (3.1)	0.091*		
Halo	41 (37.6)	38 (19.7)	<0.01		

The results are expressed as number (%); * Fisher's exact test; n, number; Se, sensitivity; Sp, specificity

ger sign were significantly specific to ($p<0.01$) and more common among mummified nodules (Table III). The specificity of these features for the differential diagnosis of thyroid cancer reached 91.7% and 99.1%, respectively; however, their sensitivity was lower.

Follow-up

There were 41 cases with follow-up data (Table IV). The follow-up duration ranged from one to nine years. The initial cystic stage was traceable in 9 cases (fig 2). All such cases were complicated cystic nodules with septation or predominantly cystic nodules. The nodule diameter and volume decreased over time and the mean volume reduction rate of the 9 nodules was 93.12%. The diameter also decreased in 41 cases with an initially solid nodule (fig 3) but there were no significant differences. A pathological specimen of a mummified nodule was also observed (fig 4). It showed a fibrous zone in the margin and necrotic erythrocytes in the interior.

Table IV. The follow-up of mummified nodules

Initial nodules	Initial diameter (cm)	End diameter (cm)	p value	VRR (%)
Cyst (n=9)	2.46±0.75	1.17±0.45	<0.01	93.12±7.31
Solid (n=32)	1.13±0.37	11.10±0.37	0.786	9.52±13.61

VRR, volume reduction rate

Discussions

In the present study, the US imaging features of mummified thyroid nodules were examined in comparison with those of malignant thyroid nodules to provide

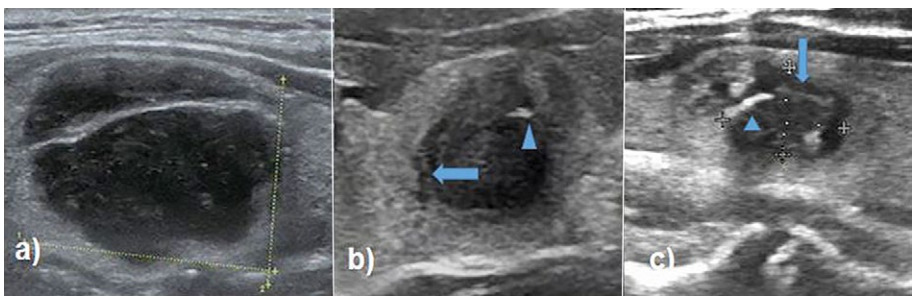

Fig 2. Necrotic process of mummified nodule formation; a) Ultrasound image obtained on 7/6/2013 showed cystic nodules in the left middle lobe, 2.8 x 2.0 cm in size; separation was observed; b) in 1/4/2017, the nodule size decreased to 1.0 x 0.8 cm, with the cystic wall shrinkage sign (arrows) and microcalcification (triangle) on the edges; (c) in 6/29/2017 the nodule size decreased to 0.9 x 0.6 cm and the range of the cystic wall shrinkage sign was reduced (arrow). The extent of calcification on the edges increased (triangle). The hypoechoic zone between the shrunken nodules and normal glands expanded to form a halo.

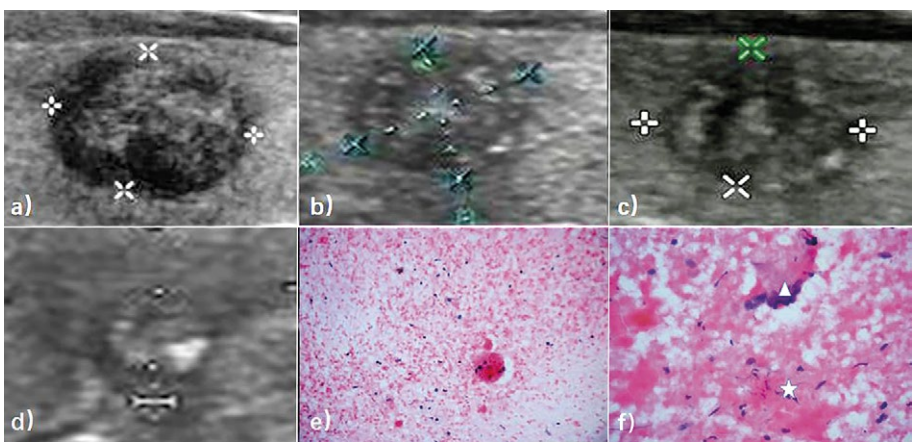

Fig 3. A nodule in the left thyroid lobe: a) The ultrasound image obtained on 6/17/2012 showed a nodule 1.1 x 0.8 cm in size; b) in 12/24/2013 the nodule had 0.8x0.6 cm and the cystic wall shrinkage sign was observed; c) in 04/12/2015 the nodule size was 0.8 x 0.6 cm and the finger sign was observed; d) in 6/15/2017 the nodule had 0.7 x 0.6 cm and calcification was observed; e) The photomicrograph (H&E staining, ×400) from 12/25/2013 showed a background of necrosis and histiocytes and no suspicious or malignant cells; (f) The photomicrograph (H&E staining, ×400) on 6/17/2017 showed multinuclear macrophages (triangle) and fibroblasts (stars).

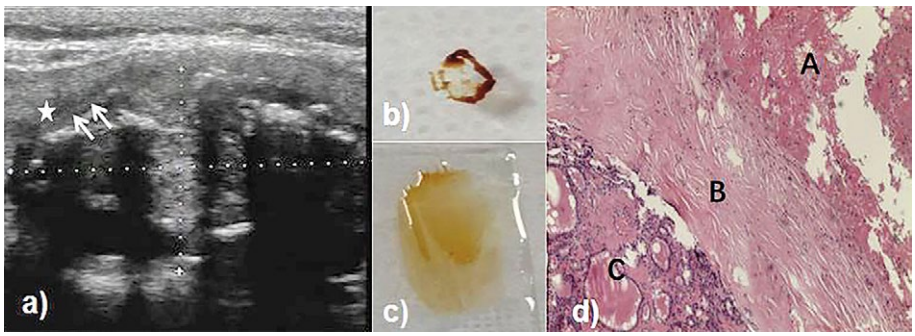

Fig 4. A nodule in the right thyroid lobe with calcification: a) the size of the nodule was 3.5 x 2.0 cm and massive calcification, a partial cystic wall shrinkage sign with hyperechoic signals (arrow) and a hypoechoic rim (star) were observed; b) the aspirates of the mummified nodules were dark brown in color; c) hardly any effective cells appeared on the slide; d) the pathological specimen was used to observe the necrotic margin; necrotic erythrocytes (A), a fibrous zone (B) and normal thyroid follicles (C) were observed.

evidence for their differential diagnosis. The cystic wall shrinkage sign and a concentric configuration or the finger sign were highly specific to mummified thyroid nodules. A previous research has suggested that central nodular thyrocyte hypoxia, nodule hemorrhage and subsequent intracystic modification may play important roles in the initiation of a scarring process that leads to the mummified appearance of such nodules on US [6]. By following patients with mummified nodules, we found cytological changes - hemosiderin was replaced by fibroblasts. We speculate that early during internal nodule repair, the absorption of necrotic material within the capsule causes the cystic volume to decrease, leading to shrinkage and ultimately collapse of the capsule wall. Over time, the necrotic material in the nodule becomes staggered between the collapsed cyst wall and the remaining active components, forming either the finger sign or a concentric circle configuration. When the arrangement of these components is irregular, the nodule is mostly characterized by interweaving regions of hyper- and hypoechogenicity. Moreover, changes in the shape of mummified nodules were observed over the course of the follow-up period, which caused the low sensitivity of these two features.

The halo sign is a nonspecific manifestation of a mummified nodule. Experts have differing opinions regarding the value of the halo sign in distinguishing benign from malignant nodules [10-14]. Lacout et al [6] considered that the halo sign is related to the development of tissue granulation and the formation of a fibrous capsule. We observed the gross pathology of a calcified mummified nodule with a halo and found a large amount of fibrous tissue at the edges of the nodule, confirming the theory presented by Lacout et al. However, this evidence is anecdotal, and additional data should be collected to confirm this finding. The halo sign was observed in 19.7% of mummified nodules and a smaller proportion of thyroid carcinoma lesions. Therefore, the halo sign cannot be used to distinguish mummified thyroid nodules from thyroid carcinoma.

Lacout et al [6] reported that eggshell calcification develops early in the cyst wall that will become a mummified thyroid nodule. Most studies have suggested that eggshell calcification is a characteristic feature of benign nodules, whereas incomplete eggshell calcification is suggestive of malignancy [15]. We found only six cases of mummified nodules showing eggshell calcification but no cases of malignant nodules with eggshell calcification. Microcalcification is generally considered to be a characteristic manifestation of malignancy [15-18] but it was also reported in dystrophic conditions and the benign thyroid nodule mummification process [19-21]. Therefore, microcalcification cannot be used as a diagnostic criterion.

The aspiration of a mummified nodule yields a characteristic viscous substance that is brown in color. Substantial pressure is required to push the viscous substance out of the biopsy needle. Under a cover slip, hardly any effective cells appear on the slide. Based on these characteristics, we can clearly diagnose mummified nodules. Therefore, puncture should be followed by detailed documentation of the characteristics of the extracted fluid/tissue. When intraoperative FNAC yields only a small number of cells, a diagnosis of mummified nodules may be done and this diagnosis should prevent the need for secondary surgery.

The present study has several limitations. First, although the mummified thyroid nodules were confirmed by FNAC, the results of the histopathological examination were obtained for only one nodule. Selection bias may have been present because of the nature of retrospective single-center studies and all of the thyroid malignant nodules were papillary carcinoma. Furthermore,

due to the stringent standards used for pathological classification, the percentage of mummified nodules was likely underestimated.

In **conclusion**, we found that mummified thyroid nodules exhibit defining characteristics, including a decreased cyst size or predominantly cystic nodules, collapse of the capsule wall and a concentric configuration or the finger sign, with a brown, viscous material, characteristic of mummified nodules, extracted by FNAC.

Conflicts of interest: none

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