

Focal Nodular Hashimoto's Thyroiditis: Comparison of Ultrasonographic Features with Malignant and Other Benign Nodules

Jun Wei Zhang, ¹MBBS (Hons), MMed (Diag Rad), FRCR, Zhao Jin Chen, ²MSc, Anil Gopinathan, ^{1,3}MD, FRCR, FAMS

Abstract

Introduction: Hashimoto's thyroiditis (HT) can present as focal nodular disease. This study aimed to determine the distinguishing sonographic features of nodules in biopsy-proven focal HT. **Materials and Methods:** The study included 388 thyroid nodules from 310 patients who underwent ultrasound-guided fine-needle aspiration biopsy (FNAB). There were 28 focal HT, 27 malignant and 333 other benign nodules. Sonographic features of focal HT nodules on prebiopsy ultrasound were compared with malignant nodules and other benign nodules using multinomial logistic regression adjusting for the correlation between multiple nodules obtained from the same patient. **Results:** Most focal HT nodules were purely solid (92.8%), iso-hyperechoic (70.4%), had regular margins (75.0%) and central vascularity (85.7%). Hypoechogenicity (29.6% vs 42.3%; $P = 0.017$) and microcalcifications (3.6% vs 44.4%; $P = 0.003$) were significantly less common in focal HT than malignant nodules. None of the focal HT nodules demonstrated marked hypoechogenicity, irregular margins or cervical lymphadenopathy, which are traditionally associated with malignancy. Compared to other benign nodules, focal HT nodules were significantly more likely to be purely solid (92.8% vs 49.0%; $P = 0.016$), ill-defined (25.0% vs 7.0%; $P = 0.004$) and lack comet-tail artefacts (92.9% vs 66.1%; $P = 0.012$), which in combination were 17.9% sensitive and 94.6% specific for focal HT. **Conclusion:** Awareness of the above-described sonographic appearances of focal HT may aid in differentiating them from malignant nodules and risk-stratify for FNAB. While there is substantial overlap with other benign nodules, a combination of the above-mentioned 3 ultrasound features is highly specific for focal HT and can prompt further serological evaluation in clinically unsuspected HT.

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Introduction

Hashimoto's thyroiditis (HT), or chronic lymphocytic thyroiditis, is the most common cause of hypothyroidism in non-iodine-deficient countries.¹ The diagnosis is usually based on clinical and serological (serum antibodies against thyroid peroxidase and thyroglobulin) findings, with a limited role for ultrasound imaging.^{2,3} Diffuse or patchy decrease in echogenicity, heterogeneous echotexture with micronodule formation, parenchymal hypervascularity and diffuse gland enlargement are the usual sonographic findings in HT.^{4,5} Other than these diffuse patterns of involvement,

HT may also present with nodular (often palpable) disease, with or without background parenchymal changes on ultrasound. This has been variably called focal or nodular HT.^{4,5} These nodules can coexist with benign hyperplastic nodules as well as with malignancy, with an increased rate of lymphoma and papillary carcinoma reported in patients with HT.^{3,6-8} Fine-needle aspiration biopsy (FNAB) is the most practical way of differentiating these entities. Meanwhile, it is not unusual for the initial diagnosis of HT to be made only after a biopsy of a thyroid nodule, suggesting a higher incidence of HT in the community than that detected from

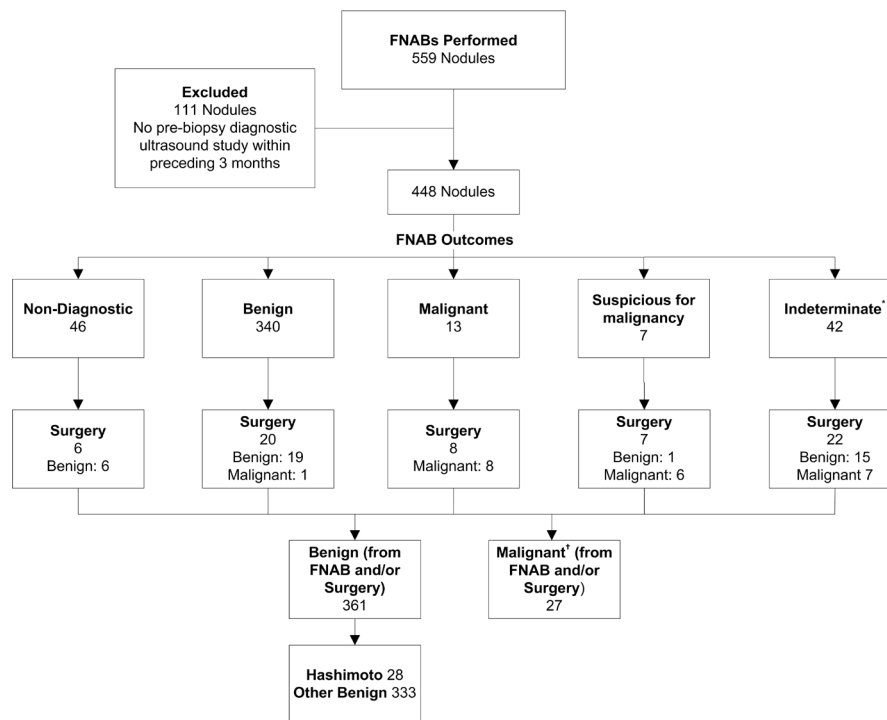
¹Department of Diagnostic Imaging, National University Hospital, Singapore

²Investigational Medicine Unit, National University Health System, Singapore

³Department of Diagnostic Radiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Address for Correspondence: Dr Anil Gopinathan, Department of Diagnostic Imaging, Level 2 Main Building, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: ivyanil10@gmail.com



* Includes follicular or Hürthle cell neoplasm, atypia or follicular lesion of undetermined significance.

† One nodule that had a benign FNAB outcome but malignant histology from surgery was classified as malignant.

Fig. 1. Distribution of different types of thyroid nodules in the study sample.

clinical evaluation and biochemistry.^{9,10} By directing the selection of nodules for FNAB, ultrasound can play a vital role in the surveillance for malignancy as well as in the potential early diagnosis of HT. However, currently there is limited data on the sonographic features of focal HT, with varying results on the features that distinguish them from malignant or other benign nodules.^{4,5,11-14} To our knowledge, there is no previous study from Singapore that has assessed the ultrasound features of focal HT in the local population.

In 559 thyroid nodules that underwent ultrasound-guided FNAB, we found that well-defined irregular margins, microcalcifications, coarse calcifications and cervical lymphadenopathy were independent sonographic predictors of malignancy, and the use of a combination of these features can help to risk-stratify nodules for FNAB with high sensitivity and specificity of 81.5% and 93.1%, respectively.¹⁵ The current study, based on the same patient cohort, aimed to describe the sonographic findings of biopsy-proven focal HT and identify features that can differentiate them from malignant or other benign nodules.

Materials and Methods

The study was performed with approval from the institutional review board. Between January 2010 and April 2013, a total of 559 ultrasound-guided thyroid nodule

FNABs were performed in the radiology department of a tertiary institution. Thyroid nodules with a tissue diagnosis (from FNAB or surgical pathology, if available) and a diagnostic ultrasound within 3 months preceding the biopsy were included in this study. Thus, the final analysis was based on 388 nodules in 310 patients (60 males, 250 females; age range, 13 to 83 years; mean age: 53 years $\pm$ 14 SD) (Fig. 1). There were 28 (7.2%) nodules with focal HT (from 24 patients), 27 (7.0%) malignant nodules (from 19 patients) and 333 (85.8%) other benign nodules (from 273 patients). Of the malignant nodules, 23 were papillary carcinomas, 2 were medullary carcinomas and 2 were lymphomas. Of the other benign nodules, 321 were hyperplastic nodules and 12 were follicular adenomas. The overall prevalence of HT in this study population based on ultrasound-guided FNAB was 7.7% (24 of 310 patients).

The FNABs were performed using a 23-25G needle under sonographic guidance in the interventional radiology suite. There was an on-site cytotechnologist available to assess the adequacy of the biopsy samples. Histological results were used in lieu of cytology if the nodule underwent subsequent surgical resection. Relevant clinical (history of HT and thyroid hormone replacement) and biochemical (thyroid profile and thyroid antibody levels) information were also retrieved from the electronic medical records.

Images of diagnostic ultrasound studies performed within 3 months preceding the FNAB were retrospectively reviewed by an attending radiologist blinded to the FNAB and histological outcomes. The thyroid nodules were assessed for the following sonographic features: size (in the longest dimension); multiplicity; consistency (purely solid, predominantly $\geq 50\%$ solid, predominantly cystic and purely cystic); echogenicity of the solid component (with reference to the thyroid parenchyma and strap muscles); margins (well-defined regular, well-defined irregular [microlobulated or speculated] and ill-defined); the presence of a hypoechoic halo; colloid (tiny echogenic foci with comet-tail artefacts); a taller-than-wide shape (anteroposterior diameter more than transverse diameter on a transverse or longitudinal plane); central vascularity; and calcifications (rim, coarse or microcalcification). Thyroid gland enlargement and background parenchymal changes of diffuse HT (reduced echogenicity equal to or lower than that of the strap muscles, and heterogeneous echotexture with micronodule formation and hypervascularity) were also sought.

Data Analysis

Statistical analyses were performed on a per nodule basis using the STATA software (version 13.0; StataCorp, College Station, Texas, USA), assuming a two-sided test with conventional significance level of 0.05. The demographic and sonographic features of focal HT were compared with those of malignant nodules and other benign nodules using multinomial logistic regression, adjusting for the correlation between multiple nodules obtained from the same patient using a clustered robust variance estimation approach by considering both variability between patients and within the same patient (at the nodule level) in the parameter estimation.

Results

Clinical and Biochemical Profile of Patients with Focal HT

Ten patients (with 12 nodules) with biopsy-proven focal HT had a known prebiopsy diagnosis of HT, of which 8 were on thyroid hormone replacement and 2 were euthyroid at the time of biopsy. Meanwhile, the remaining 14 patients (16 nodules) had their first diagnosis of HT made on ultrasound-guided FNAB. Most of them were euthyroid with only 1 hypothyroid (elevated thyrotropin [TSH] and low free thyroxine [T4] levels) patient. Antithyroglobulin and antithyroid peroxidase antibody titres were available in 19 of the 24 patients and were elevated in 16 of them (84.2%).

Background Ultrasound Features of HT

All patients with biopsy-proven focal HT had diffuse heterogeneity of the parenchymal echotexture, while 14 (58.3%) of them had the typical appearance of diffuse HT (micronodule formation, reduced parenchymal echogenicity equal to or lower than that of the strap muscles and increased vascularity) (Fig. 2). Twenty-one patients (87.5%) had an enlarged thyroid gland (anteroposterior diameter more than 18 mm)¹⁶ at ultrasound, while the rest had a normal-sized thyroid gland.

Demographic Information and Sonographic Features of Nodules in Focal HT and Comparison with Malignant and Other Benign Nodules

Among the 24 patients with HT, 23 (95.8%) of them were female. The mean age was 46 years $\pm$ 15 (SD) (range, 18 to 82 years). There was no significant difference in age and gender between patients with focal HT, malignant nodules or other benign nodules (Table 1).

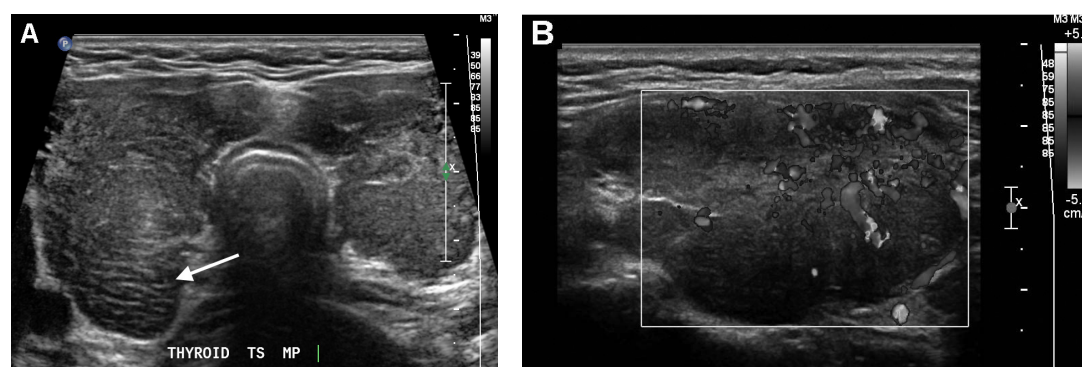


Fig. 2. A) is a transverse greyscale image of the thyroid gland from a 44-year-old woman referred for a diffuse goitre. There was no known history of HT. The thyroid gland shows diffuse asymmetrical enlargement (right lobe more than left). There are features of diffuse HT in the background parenchyma—heterogeneous echotexture with micronodule formation (arrow) and geographic areas of hypoechogenicity (comparable to that of the strap muscles). However, no discrete focal nodule is otherwise seen in this cross section. B) is a colour Doppler image of the left thyroid lobe demonstrating increased parenchymal vascularity, another feature of diffuse HT.

Table 1. Demographic and Sonographic Features of Focal HT, Malignant and Other Benign Nodules

	Nodules			Focal HT vs Malignant		Focal HT vs Other Benign	
	Focal HT (n = 28)	Malignant (n = 27)	Other Benign (n = 333)	Crude RRR* (95% CI)	P Value*	Crude RRR* (95% CI)	P Value*
Age, mean $\pm$ SD	49 $\pm$ 16	48 $\pm$ 16	55 $\pm$ 14	1.00 (0.95 to 1.05)	0.947	0.97 (0.94 to 1.00)	0.081
Female gender, no. (%) of patients	27 (96.4)	22 (81.5)	270 (81.1)	6.14 (0.56 to 66.98)	0.137	6.30 (0.83 to 48.09)	0.076
Size of nodule in mm, mean $\pm$ SD	19 $\pm$ 13	17 $\pm$ 13	24 $\pm$ 12	1.02 (0.94 to 1.11)	0.605	0.95 (0.90 to 1.01)	0.106
Internal content, no. (%)							
Purely cystic or predominantly cystic	1 (3.6)	1 (3.7)	77 (23.1)	1.00 (reference)	-	1.00 (reference)	-
Purely solid	26 (92.8)	25 (92.6)	163 (49.0)	1.04 (0.06 to 18.13)	0.979	12.29 (1.59 to 95.03)	0.016
Predominantly solid	1 (3.6)	1 (3.7)	63 (18.9)	1.00 (0.02 to 50.74)	1.000	1.22 (0.07 to 20.06)	0.888
Spongiform†	0 (0.0)	0 (0.0)	30 (9.0)	-	-	-	-
Taller-than-wide shape, no. (%)	2 (7.1)	6 (22.2)	18 (5.4)	0.27 (0.03 to 2.36)	0.236	1.35 (0.17 to 10.59)	0.778
Margins, no. (%)							
Well-defined regular	21 (75.0)	7 (25.9)	300 (90.1)	1.00 (reference)	-	1.00 (reference)	-
Well-defined irregular (microlobulated or spiculated)	0 (0.0)	16 (59.3)	8 (2.4)	-	-	-	-
Ill-defined	7 (25.0)	4 (14.8)	25 (7.5)	0.58 (0.13 to 2.69)	0.490	4.00 (1.57 to 10.16)	0.004
Echogenicity of solid component,§ no. (%)							
Isoechoic	15 (55.6)	3 (11.5)	169 (57.1)	1.00 (reference)	-	1.00 (reference)	-
Hypoechoic	8 (29.6)	11 (42.3)	85 (28.7)	0.15 (0.03 to 0.71)	0.017	1.06 (0.43 to 2.62)	0.899
Markedly hypoechoic	0 (0.0)	10 (38.5)	5 (1.7)	-	-	-	-
Hyperechoic	4 (14.8)	2 (7.7)	37 (12.5)	0.40 (0.05 to 3.24)	0.391	1.22 (0.39 to 3.80)	0.734
Solitary nodule, no. (%)	2 (7.1)	4 (14.8)	28 (8.4)	0.44 (0.05 to 3.94)	0.465	0.84 (0.18 to 3.80)	0.891
Hypoechoic halo‡, no. (%)	13 (52.0)	3 (12.0)	175 (69.2)	7.94 (1.95 to 32.34)	0.004	0.48 (0.22 to 1.04)	0.063
Calcifications, no. (%)							
No calcification	25 (89.2)	12 (44.4)	315 (94.6)	1.00 (reference)	-	1.00 (reference)	-
Microcalcifications	1 (3.6)	12 (44.4)	3 (0.9)	0.04 (0.005 to 0.33)	0.003	4.20 (0.44 to 39.64)	0.211
Rim calcifications	1 (3.6)	0 (0.0)	3 (0.9)	-	-	4.20 (0.42 to 42.24)	0.223
Coarse calcifications	1 (3.6)	3 (11.2)	12 (3.6)	0.16 (0.01 to 1.76)	0.134	1.05 (0.13 to 8.80)	0.964
Comet-tail artefacts,§ no. (%)	2 (7.1)	1 (3.9)	113 (33.9)	1.92 (0.16 to 23.38)	0.608	0.15 (0.03 to 0.66)	0.012
Central vascularity,§ no. (%)	24 (85.7)	19 (73.1)	235 (70.6)	2.21 (0.60 to 8.18)	0.235	2.50 (0.85 to 7.33)	0.094
Cervical lymphadenopathy¶ no. (%)	0 (0.0)	5 (18.5)	0 (0.0)	-	-	-	-

HT: Hashimoto's thyroiditis; RRR: Relative risk ratio; SD: Standard deviation

*Obtained using multinomial logistic regression accounting for the correlation between multiple nodules obtained from the same patient.

†No further analysis performed as spongiform consistency was only seen in other benign nodules.

‡Excluding purely cystic nodules.

§There were diffuse coarse calcifications in one malignant nodule, which prevented further assessment of echogenicity, vascularity and for presence of comet tail artefacts.

||Excluding purely cystic or predominantly cystic nodules.

¶No further analysis performed as cervical lymphadenopathy was only seen in malignant nodules.

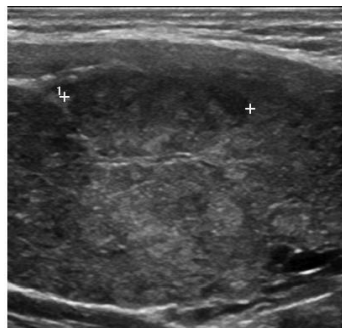


Fig. 3. Longitudinal greyscale image of cytology-proven focal HT from a 30-year-old woman with diffuse goitre. There was no known history of HT. The nodule (marked by cursors) is purely solid with ill-defined margins, isoechoic and lacks internal colloid (tiny echogenic foci with posterior comet-tail artefacts). The background parenchyma demonstrates features of diffuse HT.

Nodules in focal HT were most often purely solid (92.8%) with well-defined regular margins (75.0%) and isoechoic to the thyroid parenchyma (55.6%). A substantial minority (25.0%) had ill-defined margins (Figs. 3 and 4). Most of the nodules demonstrated central vascularity (85.7%). A hypoechoic halo was present in almost half the nodules. Colloid (comet-tail artefacts) (7.1%), a taller-than-wide shape (7.1%) and calcifications of any kind (10.8%) were infrequently seen (Table 1).

Nodules in focal HT were significantly less likely than malignant nodules to be hypoechoic (29.6% vs 42.3%; crude relative risk ratio [CRRR] = 0.15; 95% CI, 0.03 to 0.71; $P = 0.017$) or contain microcalcifications (3.6% vs 44.4%; CRRR = 0.04; 95% CI, 0.005 to 0.33; $P = 0.003$), and were more likely to have a hypoechoic halo (52.0% vs 12.0%; CRRR = 7.94; 95% CI, 1.95 to 32.34; $P = 0.004$) (Table 1). Well-defined irregular (microlobulated or spiculated) margins, marked hypoechogenicity and cervical lymphadenopathy were not seen in any nodule with focal HT but were present in 59.3%, 38.5% and 18.5% of malignant nodules, respectively.

Compared to other benign nodules, focal HT rarely had comet-tail artefacts on ultrasound (7.1% vs 33.9%; CRRR = 0.15; 95% CI, 0.03 to 0.66; $P = 0.012$). Meanwhile, they were significantly more likely to have ill-defined margins (25.0% vs 7.5%; CRRR = 4.00; 95% CI, 1.57 to 10.16; $P = 0.004$) and purely solid consistency (92.8% vs 49.0%; CRRR = 12.29; 95% CI, 1.59 to 95.03; $P = 0.016$) (Table 1).

There were 5 nodules (17.9%) with focal HT that displayed a combination of the 3 sonographic features of purely solid consistency, ill-defined margins and absence of colloid. This combination was rarely seen in other benign nodules (18 nodules; 5.4%). Using the coexistence of these 3 sonographic features as an indicator of focal HT, the diagnostic sensitivity and specificity were 17.9% and 94.6%, respectively. Four

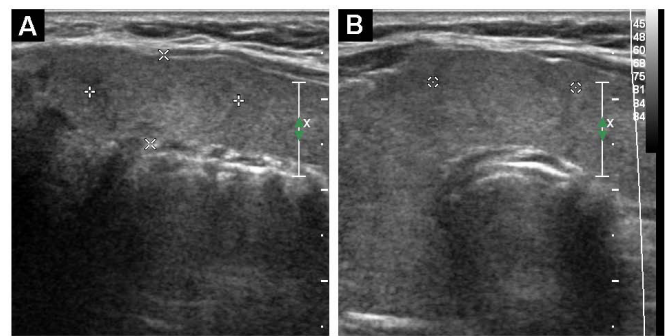


Fig. 4. A) Longitudinal greyscale image of cytology-proven focal HT from a 52-year-old woman with diffuse goitre. There was no known history of HT. The nodule (marked by cursors) is purely solid with ill-defined margins, isoechoic to the background parenchyma and lacks comet-tail artefacts. The background parenchyma is unremarkable except for subtle heterogeneity. B) Transverse greyscale image of the same nodule (marked by cursors).

of these nodules were from patients in whom FNAB led to the initial diagnosis of HT.

Discussion

On FNAB, HT demonstrates follicular atrophy, metaplastic Hürthle cells and diffuse lymphocytic infiltration in close association with follicular cells and varying degrees of fibrosis.^{2,5,17} The prevalence of HT based on ultrasound-guided FNAB in our study population was 7.7%, within the range (4% to 13.4%) quoted in previous FNAB-based studies^{4,5,10,18} and much higher than the reported clinical prevalence of HT (0.5% to 0.8 %).¹⁰ Staii et al rationalised this discrepancy with the intuitive argument that cytological diagnosis would always precede clinical diagnosis.¹⁰ We believe that the element of selection bias may also account for the higher frequency of HT in cytology-based series.

The nodules in focal HT have been described on ultrasound as hypoechoic with ill-defined margins by Takashima et al,¹³ solid and hyperechoic with ill-defined margins by Langer et al,⁴ and solid and hypoechoic with a substantial minority (40%) possessing ill-defined margins by Anderson et al.⁵ In our study, most of the focal HT nodules were solid (92.8%) and iso-hyperechoic (70.4%) with well-defined regular margins (75.0%) and central vascularity (85.7%). Diffuse heterogeneity of the background parenchyma (100%) and enlargement of the gland (87.5%) were also frequently encountered, although the typical micronodular parenchymal pattern was seen in less than 60% of our patients. Once again, this may be attributed to cytology permitting early diagnosis, which is also indicated by the euthyroid status of the majority of our patients.

The association between HT and papillary thyroid carcinoma has been widely described, with frequency of cancer between 10% to 58% on surgical pathology

series.^{7,8,12,19} The risk of thyroid lymphoma, while still very low overall, has also been reported to be up to 80 times higher in the presence of HT.^{3,6} It has therefore been recommended that FNAB be performed in patients with HT and a suspicious nodule.^{1,3} The role of ultrasound in selecting discrete thyroid nodules for biopsy in patients with HT is unclear. Some studies recommend risk stratification using ultrasound, based on previously published sonographic criteria for malignancy,^{11,12,20} while others have failed to demonstrate specific features that can differentiate focal HT from malignancy.^{4,13} Overall, our results are broadly in agreement with the former thought. Previously described sonographic features of malignancy such as hypoechogenicity, marked hypoechogenicity, irregular margins, microcalcifications and cervical lymphadenopathy are significantly more common in malignancy than focal HT. Meanwhile, other features associated with malignant nodules, such as a taller-than-wide shape and coarse calcifications were not useful in differentiating them from focal HT. This may be due to the increased fibrosis in focal HT nodules, leading to a harder consistency and decreased compressibility with a resultant taller-than-wide shape.²¹ Increased fibrosis may also account for dystrophic calcifications manifesting as coarse calcification on ultrasound.²² Central vascularity was almost equally frequent in both focal HT and malignant nodules (85.7% vs 73.1%). This may be attributed to the increased sensitivity of modern high quality scanners in detecting even mild degrees of internal vascularity in solid nodules.²²

Few studies have directly compared sonographic features of cytology-confirmed focal HT with those of other benign nodules. Anderson et al¹¹ found focal HT to be more likely solid, isoechoic, avascular and ill-defined. Fu et al found most nodules in focal HT to be hypovascular, although some of them had a specific hypervascularity that they termed 'focal thyroid inferno' (vascularity throughout the entire nodule).¹⁴ We found considerable overlap in the sonographic features of focal HT and other benign nodules, although a few interesting observations were made. Almost all the nodules in focal HT (92.8%) were purely solid, compared to less than half (49.0%) of the other benign nodules. This can be explained by considering the natural history of hyperplastic nodules in multinodular goitre, whereby cycles of exacerbation and remission have led to haemorrhage and cystic degeneration, forming cystic spaces filled with blood product and colloid.²³ The same concept also explains the rarity of comet-tail artefacts in focal HT (7.1% vs 33.9%), since this phenomenon is a signature of colloid within a thyroid nodule.²² A quarter of nodules in focal HT also had ill-defined margins, which were rarely seen in other benign nodules (7.5%). In HT, this may be due to heterogeneous background echotexture secondary to diffuse or focal inflammatory infiltration.

In our study, more than half of the patients with HT had their initial diagnosis made on ultrasound-guided FNAB. In an attempt to recognise a diagnostic imaging pattern for focal HT in relation to other benign nodules, we found that a combination of 3 greyscale sonographic characteristics (namely, purely solid consistency, ill-defined margins and absence of comet-tail artefacts) was almost 95% specific for focal HT. When present on ultrasound, these features can prompt further serological evaluation for HT in clinically unsuspected cases. This may be especially useful when there are no background parenchymal features of HT. An early diagnosis of HT may be particularly valuable in women of child-bearing age, since maternal thyroid status has a major impact on the fetal outcome as well as on the well-being of the newborn.²⁴ However, the usefulness of this combination of sonographic features is limited by its low sensitivity (17.9%).

There are limitations to our study. There is selection bias as the nodules in our study population have been referred for FNAB only after diagnostic ultrasound, and may have been assessed to be of a higher risk of malignancy from clinical history or imaging features. A relatively small number of focal HT and malignant nodules have been compared with a large number of other benign nodules. However, it may be argued that this reflects the practical clinical scenario. The ultrasound images were assessed by a single radiologist. Nevertheless, previous studies have reported fair to substantial interobserver agreement for the assessment of greyscale and Doppler sonographic features.²⁵⁻²⁷ We relied on cytological outcomes instead of surgical pathology to assign most of the diagnoses. However, the high diagnostic accuracy of thyroid nodule FNAB is well-acknowledged.²⁸

Conclusion

Most focal HT nodules are purely solid and iso-hyperechoic with well-defined margins and central vascularity. Previously described sonographic criteria for malignancy remain useful in distinguishing malignant nodules from focal HT and can be used to risk-stratify nodules for FNAB in the ultrasound follow-up of HT. However, some features associated with a malignant nodule (namely, a taller-than-wide shape, coarse calcifications and central vascularity) may be less useful. While there is substantial overlap in sonographic features with other benign nodules, a combination of purely solid consistency, ill-defined margins and absence of comet-tail artefacts is highly specific for focal HT. This can prompt further serological evaluation and possible early diagnosis of clinically unsuspected HT, although its value is limited by low sensitivity.

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