Hashimoto Thyroiditis: Part 1, Sonographic Analysis of the Nodular Form of Hashimoto Thyroiditis

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OBJECTIVE. The purpose of this article is to analyze the sonographic appearance of nodular Hashimoto thyroiditis.

SUBJECTS AND METHODS. As part of an ongoing multiinstitutional study, patients who underwent ultrasound examination and fine-needle aspiration of one or more thyroid nodules were analyzed for multiple predetermined sonographic features. Patients completed a questionnaire, including information about thyroid function and thyroid medication. Patients (n = 61) with fine-needle aspiration cytologic results consistent with nodular Hashimoto thyroiditis (n = 64) were included in the study.

RESULTS. The mean (± SD) diameter of nodular Hashimoto thyroiditis was 15 ± 7.33 mm. Nodular Hashimoto thyroiditis occurred as a solitary nodule in 36% (23/64) of cases and in the setting of five or more nodules in 23% (15/64) of cases. Fifty-five percent (35/64) of the cases of nodular Hashimoto thyroiditis occurred within a sonographic background of diffuse Hashimoto thyroiditis, and 45% (29/64) of cases occurred within normal thyroid parenchyma. The sonographic appearance was extremely variable. It was most commonly solid (69% [42/61] of cases) and hypoechoic (47% [27/58] of cases). Twenty percent (13/64) of nodules had calcifications (seven with nonspecific bright reflectors, four with macrocalcifications, and three eggshell), and 5% (3/64) of nodules had colloid. Twenty-seven percent (17/64) of nodules had a hypoechoic halo. The margins were well defined in 60% (36/60) and ill defined in 40% (24/60) of nodules. On Doppler analysis, 35% (22/62) of nodules were hypervascular, 42% (26/62) were isovascular or hypovascular, and 23% (14/62) were avascular.

CONCLUSION. The sonographic features and vascularity of nodular Hashimoto thyroiditis were extremely variable.

Keywords: Hashimoto thyroiditis, thyroid cytology, thyroid nodules, thyroid ultrasound

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Hashimoto thyroiditis, also known as chronic autoimmune lymphocytic thyroiditis, is a disease with a typical clinical presentation of painless diffuse enlargement of the thyroid gland accompanied by hypothyroidism and thyroid autoantibodies [1]. The sonographic appearance of Hashimoto thyroiditis is well recognized. The gland is often diffusely enlarged, and the parenchyma is coarsened, hypoechoic, and often hypervascular [2–5]. A micronodular pattern on ultrasound is highly diagnostic of Hashimoto thyroiditis with a positive predictive value of 95% [2]. Discrete nodules may, however, also occur within diffusely altered parenchyma or within sonographically normal parenchyma. The nodular form of Hashimoto thyroiditis has not received nearly as much analysis as the diffuse form, and the reported findings have been variable [2, 6, 7]. The objective of this study was to determine the extent to which there is a typical sonographic appearance to nodular Hashimoto thyroiditis.

Subjects and Methods

Subjects

Patients from six geographically diverse U.S. medical centers were included in our HIPAA-compliant study, which was approved by the institutional review boards of each participating institution. All patients at least 18 years old who underwent diagnostic thyroid ultrasound examinations and ultrasound-guided fine-needle aspirations of a focal nodule between August 2006 and December 2007 and who signed a consent form were eligible for the study. A nodule was defined as an intrathyroidal lesion of any size that was sonographically distinct from the surrounding thyroid tissue. During this period, 1,522 patients were enrolled in the study.

Society of Radiologists in Ultrasound guidelines were followed in determining which nodules were selected for fine-needle aspiration [8].

Of the total 1,522 patients, 61 (4%) had nodules that were cytologically proven to be nodular Hashimoto thyroiditis and were included in the study. Before their fine-needle aspiration, each study patient filled out a clinical data questionnaire, which included questions concerning clinical symptoms, a family history of thyroid cancer, a prior diagnosis of hypothyroidism, and treatment with thyroid replacement hormone. Patients were not questioned about whether they had a specific diagnosis of Hashimoto thyroiditis.

Pathologic Analysis

Patients were included in the study if their cytology samples were read as Hashimoto thyroiditis or chronic lymphocytic thyroiditis. For all patients for whom more than one nodule was biopsied, the cytology report, sonographic report, and sonographic images were compared to ensure that the proper nodule was analyzed. The procedure for specimen procurement was left up to the discretion of the physician performing the fine-needle aspiration. The physician was free to obtain the number of needle passes deemed appropriate at their institution. Immediate analysis of the specimen was also obtained at the discretion of the physician performing the biopsy. The cytologic interpretations from each institution were considered the reference standard for diagnosis of Hashimoto thyroiditis, and slides were not reevaluated at a central site.

Sonographic Analysis

Ultrasound images of the nodules were obtained in a prospective manner with attention focused on a preselected set of sonographic features. Ultrasound technologists at each institution were informed of these specific sonographic features and were instructed to obtain dedicated images in both the longitudinal and transverse planes that displayed these features. Digital copies of the ultrasound examinations from all the institutions were then reviewed retrospectively by two radiologists at the central site in a blinded manner. Fifty cases were reviewed jointly by both radiologists to standardize the sonographic analysis of the nodules. These 50 cases were from the larger study, not specifically from the subset of patients included in this study. The remaining cases were reviewed independently by one of these two radiologists.

The nodules were measured with the lengths corresponding to the long axis measurements on sagittal views and with the widths and thicknesses corresponding to the long and short axis measurements on transverse views. Each nodule was assessed for its percentage of solid versus cystic elements (i.e., entirely or almost entirely solid, 50–95% solid, 1–49% solid, or entirely cystic). Any nodule found to be complex was categorized as a spongelike lesion, a cyst with mural nodule, a cyst with thick wall, a cyst with multiple septations, or a lesion with scattered cystic regions in a solid background. Each nodule was also assessed for the dominant echogenicity of its solid noncalcified elements compared with adjacent thyroid parenchyma (i.e., hyperechoic, isoechoic, mildly hypoechoic, or moderately or very hypoechoic) and for the echotexture of any solid noncalcified component (i.e., homogeneous or heterogeneous).

The nodules were also assessed for the presence or absence of a hypoechoic halo (i.e., no halo, thin and regular halo, or thick or irregular halo) and for calcifications (i.e., none, micro, macro, peripheral or eggshell, or tiny nonspecific nonshadowing bright reflectors) and colloid. The category of tiny nonspecific bright reflectors was used when it was unclear whether the reflector was due to microcalcification or colloid. Colloid was diagnosed if tiny bright reflectors with a clear-cut comet-tail artifact were present. The distinctness of demarcation between the margin of the nodule and adjacent thyroid tissue was classified as well defined or ill defined. The shape of the nodule margin was also classified as smooth or lobulated. In some nodules, a particular feature could not be analyzed. For instance, in a nodule with dense peripheral calcification, the internal contents of the nodule could not be seen well enough to determine echogenicity or percentage of solid versus cystic components. Therefore, the denominators shown in the Results section and in the tables are not uniform

Color or power Doppler ultrasound or both was used to evaluate whether the nodule was hypervascular, isovascular, or hypovascular compared with adjacent thyroid parenchyma. The distribution of the flow was also assessed (i.e., central and peripheral, only central, or only peripheral).

The total number of nodules in the thyroid was also recorded as one nodule (i.e., only the analyzed nodule), two to four nodules, or five or more nodules. There was no minimum size required for a nodule to be included in the total nodule count, but purely cystic nodules were excluded from the count. In the case of some nodules, a particular sonographic parameter was not recorded if it was impossible to analyze with confidence. Purely cystic nodules were not biopsied and were therefore not included in the study.

Nodules were also categorized into seven different sonographic patterns [9]—entirely or almost entirely solid and hypoechoic, entirely or almost entirely solid and isoechoic, entirely or almost entirely solid and hyperechoic, entirely or almost entirely solid with a hypoechoic halo, spongelike, complex cystic (i.e., septated cyst, thick walled cyst, or cyst with mural nodule), and solid with scattered cystic spaces.

In addition to the nodule analysis, the thyroid parenchyma was analyzed for sonographic signs of diffuse Hashimoto thyroiditis, including decreased echogenicity, heterogeneity, hypervascularity, presence of micronodules, and echogenic septations.

Data Analysis

The data were analyzed to determine the typical sonographic appearance of nodular Hashimoto thyroiditis ($n = 64$), including nodules with and without sonographic evidence of background diffuse Hashimoto thyroiditis. Next, the sonographic features of nodular Hashimoto thyroiditis within backgrounds of diffuse Hashimoto thyroiditis ($n = 35$) were compared with the features of nodular Hashimoto thyroiditis within normal thyroid parenchyma ($n = 29$). This comparison helped to determine the extent to which nodular Hashimoto thyroiditis has a different appearance within a background of diffuse Hashimoto thyroiditis. To determine whether the differences between the groups of nodules were statistically significant, the z test was used to compare the proportion of nodules possessing each sonographic feature. This resulted in a z value for each comparison, and the corresponding p value for each z value was determined from a standard normal table. Because of multiple comparisons ($n = 38$), a Bonferroni adjustment (to $\alpha = 0.05$) was performed, with the resulting value being 0.0013; thus a p value less than 0.0013 was considered statistically significant.

The length, width, and thickness of each nodule were averaged to find a mean diameter of the nodule. Maximum and minimum diameters were also determined for each nodule. The mean, maximum, and minimum diameters among all the nodules in each group were averaged. This allowed the mean, maximum, and minimum diameters to be compared among the groups using a Student's t test. If the Student's t test produced a p value less than $\alpha = 0.0013$, the difference between the means of the two groups being compared was considered statistically significant.

Results

Clinical Data

There were 64 nodules in 61 patients included in the study. Thirty-five (55%) of 64 nodules were present within a background of diffuse Hashimoto thyroiditis, and 29 (45%) were not. The median age of the patients was 49 years (range, 28–87 years). Fifty-four (89%) of the 61 patients were women. Seventeen (28%) of 61 patients reported that they had

TABLE 1: Sonographic Features of Nodular Hashimoto Thyroiditis (HT) and Comparison of Sonographic Features of NHT With and Without Diffuse Background Parenchymal HT

Nodule Characteristics	% of Nodules (No./Total No.) With			p[a]
	Nodular HT	Nodular HT Without Background HT	Nodular HT With Background HT	
Solid vs cystic				
Solid	68.9 (42/61)	48.1 (13/27)	85.3 (29/34)	0.0010
50–95% Solid	23.0 (14/61)	37.0 (10/27)	11.8 (4/34)	0.0099
1–49% Solid	8.2 (5/61)	14.8 (4/27)	2.9 (1/34)	0.0465
Echogenicity				
Hyperechoic	32.8 (19/58)	20.0 (5/25)	42.4 (14/33)	0.0359
Isoechoic	20.7 (12/58)	28.0 (7/25)	15.2 (5/33)	0.1151
Mild hypoechoic	17.2 (10/58)	20.0 (5/25)	15.2 (5/33)	0.3156
Moderate or very hypoechoic	29.3 (17/58)	32.0 (8/25)	27.3 (9/33)	0.3483
Echotexture				
Homogeneous	54.2 (32/59)	44.0 (11/25)	61.8 (21/34)	0.0885
Heterogeneous	45.8 (27/59)	56.0 (14/25)	38.2 (13/34)	0.0885
Halo				
None	71.9 (46/64)	86.2 (25/29)	60.0 (21/35)	0.0102
Thin and regular	26.6 (17/64)	13.8 (4/29)	37.1 (13/35)	0.0174
Thick or irregular	1.6 (1/64)	0 (0/29)	2.9 (1/35)	0.1788
Calcifications				
None	75.0 (48/64)	62.0 (18/29)	85.7 (30/35)	0.0150
Bright reflectors	10.9 (7/64)	17.2 (5/29)	5.7 (2/35)	0.0708
Macro	6.3 (4/64)	6.9 (2/29)	5.7 (2/35)	0.4247
Micro	0 (0/64)	0 (0/29)	0 (0/35)	0.5000
Eggshell	4.7 (3/64)	10.3 (3/29)	0 (0/35)	0.0262
Colloid	4.7 (3/64)	6.9 (2/29)	2.9 (1/35)	0.2236
Margins				
Well defined	60.0 (36/60)	70.4 (19/27)	51.5 (17/33)	0.0694
Ill defined	40.0 (24/60)	29.6 (8/27)	48.5 (16/33)	0.0694
Smooth	91.5 (54/59)	96.3 (26/27)	87.5 (28/32)	0.1131
Lobulated	8.5 (5/59)	3.7 (1/27)	12.5 (4/32)	0.1131
Doppler				
Hypervascular	35.5 (22/62)	28.6 (8/28)	41.2 (14/34)	0.1515
Isovascular or hypovascular	41.9 (26/62)	42.9 (12/28)	41.2 (14/34)	0.4483
No flow	22.6 (14/62)	28.6 (8/28)	17.6 (6/34)	0.1539
No. of nodules				
1	35.9 (23/64)	17.2 (5/29)	51.4 (18/35)	0.0023
2–4	40.6 (26/64)	55.2 (16/29)	28.6 (10/35)	0.0154
> 5	23.4 (15/64)	27.6 (8/29)	20.0 (7/35)	0.2389
Total no. of nodules	64	29	35	—

Note—When a particular feature could not be determined, the denominators are less than the total number of nodules in that category.

[a]Nodular HT without versus nodular HT with background HT. $p < 0.0013$ was considered statistically significant.

hypothyroidism, and 23 (38%) received thyroid replacement hormone. The nodule was detected by palpation in 27 patients (44%), by ultrasound examination in 16 (26%), by CT in nine (15%), by PET in two (3%), by MRI in two (3%), and by multiple techniques in five patients (8%). Seven patients (11%) reported hoarseness, nine (15%) reported difficulty swallowing, nine (15%) reported that the nodule was increasing in size, and five (8%) reported that the nodule was painful.

One clinical finding that differed between nodular Hashimoto thyroiditis within diffuse Hashimoto thyroiditis and nodular Hashimoto thyroiditis without diffuse Hashimoto thyroiditis was the number of patients reporting hypothyroidism and the use of thyroid replacement hormone. Patients with nodular Hashimoto thyroiditis in a sonographic background of diffuse Hashimoto thyroiditis were more likely to report having hypothyroidism (43%) and receiving thyroid hormones (51%) than were patients with nodular Hashimoto thyroiditis without a background of Hashimoto thyroiditis (10% with hypothyroidism and 17% receiving thyroid hormones).

Sonographic Appearance of Nodular Hashimoto Thyroiditis

The sonographic features of all nodular Hashimoto thyroiditis (n = 64), combining those with and without a background of diffuse Hashimoto thyroiditis, are summarized in Table 1, and the sizes are summarized in Table 2. The sonographic patterns of all nodular Hashimoto thyroiditis are summarized in Table 3. The average mean (± SD) diameter of nodular Hashimoto thyroiditis was 15.3 ± 7.33 mm, the average maximum diameter was 19.5 ± 10.39 mm, and the average minimum diameter was 11.5 ± 5.63 mm. Nodular Hashimoto thyroiditis occurred as a solitary nodule in 36% (23/64) of cases and occurred with five or more additional nodules in 23% (15/64) of cases.

The sonographic appearance of nodular Hashimoto thyroiditis was extremely variable. Nodular Hashimoto thyroiditis was, however, most commonly solid (69% [42/61]) and hypoechoic (47% [27/58]) (Figs. 1 and 2). Of the nodules with cystic elements, only five (26%) of 19 had less than a 50% solid component (Fig. 3). A thin hypoechoic halo was seen in 27% (17/64) of nodular Hashimoto thyroiditis (Fig. 4). Twenty percent (13/64) had calcifications. Six had nonspecific bright reflectors, three had macrocalcifications, three had eggshell calcifications, and one had both nonspecific bright

TABLE 2: Nodule Size of All Nodular Hashimoto Thyroiditis (HT) and Comparison of Nodule Size Among Nodular HT With and Without Background HT

Parameter	Nodule Diameter (mm), Mean (SD)			p^a
	All NHT	Nodular HT Without Background HT	Nodular HT With Background HT	
Average	15.3 (7.33)	15.5 (7.26)	15.0 (7.49)	0.398
Maximum	19.5 (10.39)	19.6 (10.41)	19.4 (10.53)	0.471
Minimum	11.5 (5.63)	11.9 (6.02)	11.2 (5.35)	0.322

[a]Nodular HT with vs. nodular HT without background HT. $p < 0.0013$ was considered statistically significant.

TABLE 3: Sonographic Patterns of Nodular Hashimoto Thyroiditis (HT) and Comparison of Sonographic Patterns of Nodular HT With and Without Background HT

Pattern	% of Nodules (No./Total No.) With			p^a
	All NHT	Nodular HT Without Background HT	Nodular HT With Background HT	
Solid hypoechoic	26.6 (17/64)	20.7 (6/29)	31.4 (11/35)	0.1660
Solid isoechoic	4.7 (3/64)	3.4 (1/29)	5.7 (2/35)	0.3336
Solid hyperechoic	7.8 (5/64)	3.4 (1/29)	11.4 (4/35)	0.1190
Solid with halo	23.4 (15/64)	13.8 (4/29)	31.4 (11/35)	0.0485
Spongelike	6.3 (4/64)	6.9 (2/29)	5.7 (2/35)	0.4247
Complex cystic	20.3 (13/64)	37.9 (11/29)	5.7 (2/35)	0.0007
Solid, with cystic areas	10.9 (7/64)	13.8 (4/29)	8.6 (3/35)	0.2514

[a]Nodular HT with vs. nodular HT without background HT. $p < 0.0013$ was considered statistically significant.

reflectors and macrocalcifications. Five percent (3/64) had colloid. None of the nodules had bright reflectors typical of microcalcifications.

Most nodular Hashimoto thyroiditis nodules had margins that were well defined (60% [36/60]) (Figs. 1, 3, and 4), but a substantial minority had ill-defined margins (40% [24/60]) (Figs. 2 and 5). Echogenicity, echotexture, and definition of the margin were extremely variable. The degree of vascularity was also variable: 36% (22/62) were hypervascular (Fig. 6), 42% (26/62) were isovascular or hypovascular (Fig. 7), and 23% (14/62) were avascular. Of the nodules with blood flow present, 86% had both central and peripheral flow. Because this constituted most of the nodules, the distribution of the flow was not further analyzed.

The most common patterns seen in nodular Hashimoto thyroiditis were solid hypoechoic nodules (27% [17/64]) (Figs. 1 and 2), solid nodules with a halo (23% [15/64]) (Figs. 4, 6, and 7), and complex cystic nodules (20% [13/64]) (Fig. 3). The spongelike pattern was seen in 6% (4/64) of nodules.

Comparison of Nodular Hashimoto Thyroiditis Within and Without Diffuse Hashimoto Thyroiditis

Thirty-five nodular Hashimoto thyroiditis nodules (55%) occurred within a sonographic background of diffuse Hashimoto thyroiditis (Figs. 3–7), and 29 (45%) occurred within sonographically normal thyroid parenchyma (Figs. 1 and 2). Table 1 shows the proportion of nodular Hashimoto thyroiditis, both with and without diffuse Hashimoto thyroiditis, having each of the sonographic features; these proportions were compared using a *z* test, and the resulting *p* values are shown in the far-right column. Table 2 shows the mean diameters of nodular Hashimoto thyroiditis, both with and without diffuse Hashimoto thyroiditis; the mean diameters were compared using a Student's *t* test, and the resulting *p* values are shown in the far-right column. Table 3 shows the proportion of nodular Hashimoto thyroiditis, both with and without diffuse Hashimoto thyroiditis, fitting into each of the sonographic patterns; these proportions were also compared using a *z* test, and the resulting *p* values are shown in the far-right column.

Within a background of diffuse Hashimoto thyroiditis, nodular Hashimoto thyroiditis was more likely to be solid, to be hyperechoic, to have a thin regular hypoechoic halo, to have no calcifications, and to occur as a solitary nodule. In fact, the nodule analyzed was the only thyroid nodule in 51% (18/35) of cases. On the other hand, nodular Hashimoto thyroiditis within normal thyroid parenchyma was more likely to have some cystic elements and to have peripheral eggshell calcifications. Nodular Hashimoto thyroiditis within normal parenchyma was also more likely to have additional focal nodules, and only 17% (5/29) occurred as a solitary nodule. Of these differences, only solid composition was statistically significant.

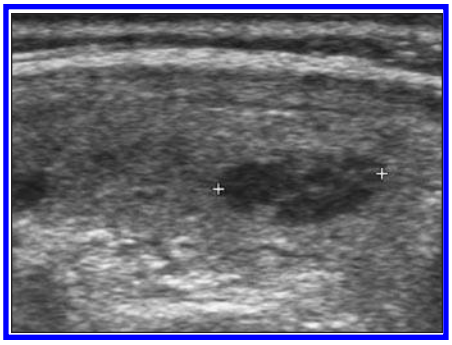

Fig. 1—63-year-old woman with nodular Hashimoto thyroiditis. Longitudinal scan shows solid hypoechoic slightly heterogeneous sharply marginated nodule (*cursors*). Background parenchyma is normal.

Fig. 2—45-year-old woman with nodular Hashimoto thyroiditis. Longitudinal scan shows solid hypoechoic homogeneous poorly marginated nodule (*cursors*). Background parenchyma is normal.

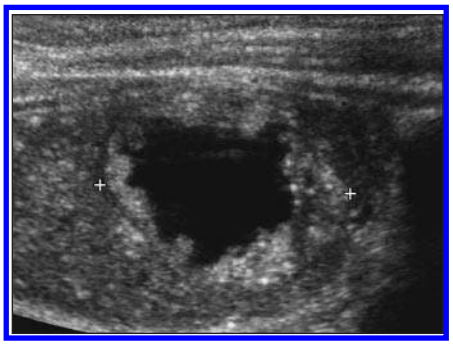

Fig. 3—83-year-old woman with nodular Hashimoto thyroiditis. Longitudinal scan shows complex predominantly cystic nodule (*cursors*) with irregular hyperechoic wall. Background parenchyma is hypoechoic and coarsened.

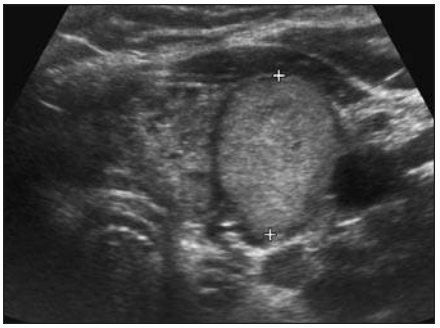

Fig. 4—37-year-old woman with nodular Hashimoto thyroiditis. Transverse scan shows solid hyperechoic homogeneous sharply marginated nodule (*cursors*) with thin hypoechoic halo. Background parenchyma is micronodular.

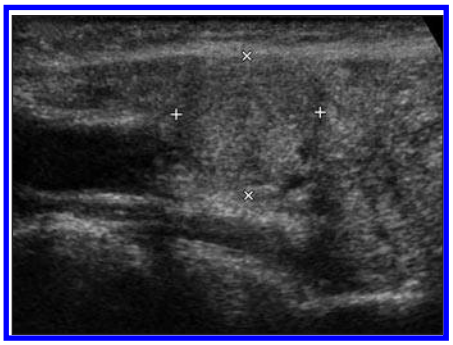

Fig. 5—61-year-old woman with nodular Hashimoto thyroiditis. Longitudinal scan shows subtle solid isoechoic homogeneous poorly marginated nodule (*cursors*). Background parenchyma is heterogeneous and hypoechoic. Nodule was more evident on real-time imaging and on color Doppler imaging.

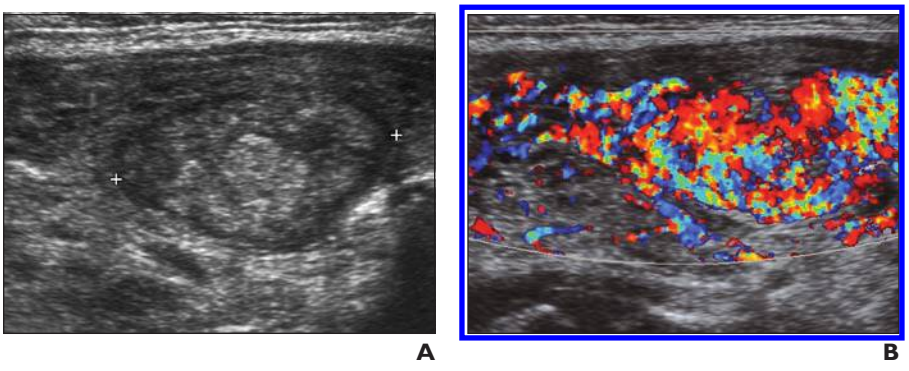

Fig. 6—32-year-old woman with nodular Hashimoto thyroiditis.
A, Longitudinal scan shows solid isoechoic heterogeneous sharply marginated nodule (*cursors*) with thin hypoechoic halo. Background parenchyma is heterogeneous and hypoechoic.
B, Longitudinal color Doppler scan shows that nodule is hypervascular compared with adjacent parenchyma.

Discussion

Hashimoto thyroiditis is an autoimmune thyroid disease that involves infiltration of the thyroid by T and B cells that are reactive to thyroid antigens. The activated B cells secrete thyroid autoantibodies, including antibodies to thyroglobulin, thyroid peroxidase, and the thyrotropin (thyroid-stimulating hormone) receptor. The cytotoxic T cells are largely responsible for the destruction of the thyroid parenchyma, leading to initial thyrotoxicosis followed by hypothyroidism [10, 11]. This inflammatory process results in the typical histopathologic appearance of Hashimoto thyroiditis, which includes lymphocyte aggregates with germinal centers, small thyroid follicles with sparse colloid, oxyphilic changes of epithelial cells, and variable fibrosis [11–13]. Although the exact cause of this thyroid autoimmunity is unknown, it is thought that Hashimoto thyroiditis develops in genetically predisposed individuals who are exposed to an environmental trigger. Several autoimmune thyroid disease susceptibility genes have been identified in prior studies [14].

Hashimoto thyroiditis is the most common cause of hypothyroidism in the United States [1]. Studies report that it is up to 15 times more common among women than men and affects at least 2% of all women [1, 15]. It has a peak incidence between the ages of 30 and 50, and other autoimmune disorders may coexist with Hashimoto thyroiditis [16]. Hashimoto thyroiditis can present clinically as painless firm diffuse goiter often accompanied by hypothyroidism and autoantibodies [1]. Patients may also present with weight gain, myxedema, fatigue, and mental slowness as a result of hypothyroidism [17]. The clinical diagnosis is confirmed by low serum T4 levels, high thyroid-stimulating hormone levels, and the presence of autoantibodies to thyroglobulin and thyroid peroxidase [1, 18]. The clinical and serological presentation is, however, extremely variable. It is not rare for patients with Hashimoto thyroiditis to have neither symptoms nor physical signs [17, 18]. In addition, prior studies have reported that autoantibodies are absent in 13% and low in 17% of patients with Hashimoto thyroiditis and are present in 2–20% of the population without thyroid disease [17]. In fact, if only clinical and serum findings were used to diagnose Hashimoto thyroiditis, the diagnosis would be missed in at least half of patients [18]. The sensitivity and specificity improve dramatically by combining ultrasound evaluation with clinical and serological assessments [17, 18]. The most accurate method of diagnosing Hashimoto thyroiditis, however, remains biopsy and histologic study [12].

The typical sonographic appearance of diffuse Hashimoto thyroiditis is now well recognized, and these features were used in our study to identify patients with diffuse Hashimoto thyroiditis. On sonography, a thyroid gland affected by Hashimoto thyroiditis typically has a diffusely altered parenchyma. The thyroid is often enlarged and hypoechoic with a heterogeneous echotexture and echogenic septations [2–6]. The decreased echogenicity is a result of lymphocyte infiltration and often correlates with hypothyroidism [19]. In the present study, 43% of patients with sonographic evidence of diffuse Hashimoto thyroiditis, including decreased echogenicity, reported that they had hypothyroidism. Another sonographic feature that has been reported to be highly diagnostic of Hashimoto thyroiditis is the presence of micronodules, which has a positive predictive value of 95%. These micronodules have been reported to range from 1 to 7 mm in size [2]. They are hypoechoic as a result of lymphocyte infiltration and have an echogenic rim due to fibrous strands throughout the thyroid parenchyma [2]. On color Doppler, the thyroid parenchyma can vary from slightly hypervascular to markedly hypervascular [20]. This increased vascularity seems to be associated with the development of hypothyroidism, which may be due to the trophic stimulation of thyroid-stimulating hormone [20].

In addition to the diffuse form, Hashimoto thyroiditis may form discrete nodules within a diffusely altered parenchyma or within a sonographically normal thyroid parenchyma [20, 21]. This second form of Hashimoto thyroiditis, also known as nodular Hashimoto thyroiditis, focal lymphocytic thyroiditis, or pseudotumor, has an incidence of approximately 5% among nodules biopsied in previous studies [7] as well as in the present study. Some authors have suggested that nodular Hashimoto thyroiditis is an early presentation

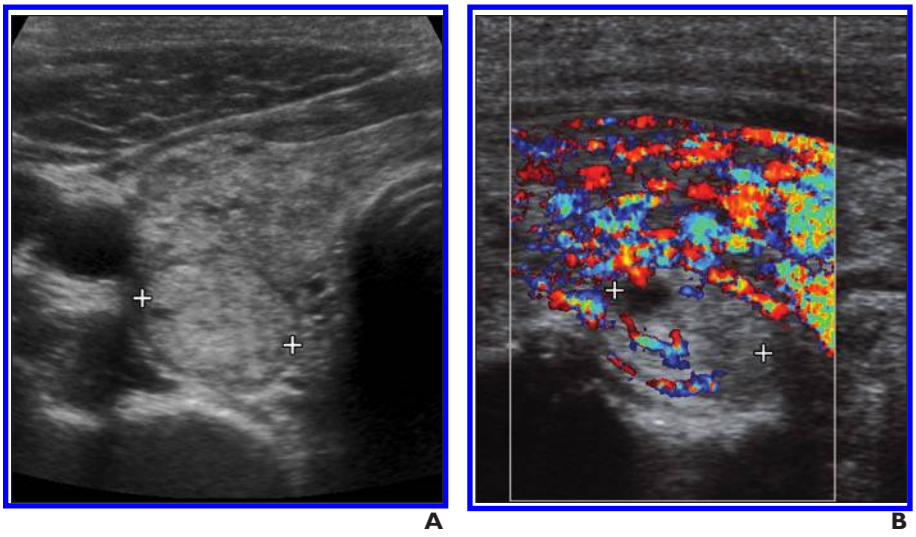

Fig. 7—49-year-old man with nodular Hashimoto thyroiditis.
A, Transverse scan shows solid isoechoic homogeneous sharply marginated nodule (*cursors*) with thin hypoechoic halo. Background parenchyma is heterogeneous and micronodular.
B, Longitudinal color Doppler scan shows that nodule (*cursors*) is hypovascular compared with adjacent parenchyma.

of Hashimoto thyroiditis [22]. Others think, however, that it is a completely different clinical form of Hashimoto thyroiditis [23]. The results of the present study cannot confirm either of these theories, but we did find that there was a much lower incidence of hypothyroidism (10%) among patients with only the nodular form of Hashimoto thyroiditis (and no sonographic evidence of diffuse Hashimoto thyroiditis) than that (43%) among patients with nodular Hashimoto thyroiditis and diffuse Hashimoto thyroiditis. This finding does suggest that isolated nodular Hashimoto thyroiditis is a clinically less severe form of the disease than is diffuse Hashimoto thyroiditis.

Few studies have investigated the sonographic appearance of nodular Hashimoto thyroiditis. Those identified by our literature search included Yeh et al. [2], Takashima et al. [6], and Langer et al. [7]. The findings of these three studies were variable. Yeh et al. [2] focused their study on the micronodular pattern of diffuse Hashimoto thyroiditis, but they found eight cytologically confirmed cases of nodular Hashimoto thyroiditis. On the basis of these eight cases, they concluded that the sonographic findings of nodular Hashimoto thyroiditis were varied and nonspecific [2]. Takashima et al. assessed the sonographic findings of all thyroid nodules in patients with clinically or pathologically proven diffuse Hashimoto thyroiditis in their retrospective study. They found that pseudotumors constituted 23% (25/107) of the sonographically detected nodules. They described nodular Hashimoto thyroiditis as hypoechoic with ill-defined margins [6]. The most recent study was the retrospective study by Langer et al. They investigated the sonographic appearance of 21 focal thyroid nodules (in 20 patients) that were proven by fine-needle aspiration to be nodular Hashimoto thyroiditis. Most (86% [18/21]) of the nodules showed sonographically evident Hashimoto thyroiditis in the background. They found that the most common appearance was a solid hyperechoic nodule with irregular margins. Cystic changes were present in three (14%) of 21 nodules. Calcifications were found in five nodules (24%), coarse shadowing calcifications were found in two nodules (10%), and nonspecific bright reflectors were found in three nodules (14%). On Doppler ultrasound, the vascularity was markedly variable with no distinguishing pattern [7].

The results of the present study agree with those of Langer et al. [7] in that most nodular Hashimoto thyroiditis nodules were solid, but a substantial minority had some cystic components. We also found a similar percentage of nodular Hashimoto thyroiditis nodules to have calcifications. Although most nodular Hashimoto thyroiditis nodules in our study had margins that were well defined and smooth, there was a substantial minority with ill-defined margins. We found the echogenicity of nodular Hashimoto thyroiditis to be variable, but there were more hypoechoic nodules than hyperechoic or isoechoic nodules. Similar to previous results [7], the vascularity of nodular Hashimoto thyroiditis in our study was variable. Interestingly, despite the typical finding of hypervascularity with diffuse Hashimoto thyroiditis, a substantial minority of nodular Hashimoto thyroiditis nodules had no demonstrable flow.

Nodular Hashimoto thyroiditis was shown to share certain features that have been previously documented to correlate highly with benign cytology [20, 24–28]. These include spongelike appearance (n = 4), greater than 50% cystic components (n = 5), hyperechoic echogenicity (n = 19), and a thin regular halo (n = 17).

On the other hand, nodular Hashimoto thyroiditis also displayed certain sonographic features that are reported to be predictive of malignant thyroid nodules. This finding is particularly troublesome, because numerous studies have reported a strong association between Hashimoto thyroiditis and primary thyroid lymphoma [29–32]. In addition, although still controversial, there is evidence suggesting that there is an increased risk of papillary thyroid carcinoma among patients with Hashimoto thyroiditis [23, 33, 34]. A large majority of thyroid cancers and lymphoma are solid hypoechoic nodules [20, 24–28, 32, 35]. Unfortunately, 27% (17/64) of our cases of nodular Hashimoto thyroiditis displayed these findings. Lobulated margins, a thick or irregular halo, and hypervascularity are additional features reported to be suspicious for malignancy [20, 24–28, 35]. These features were seen in 9% (5/59), 2% (1/64), and 36% (22/62) of our nodular Hashimoto thyroiditis cases, respectively. This overlap in the sonographic appearance of nodular Hashimoto thyroiditis and malignant nodules underscores the difficulty in distinguishing the two.

The discussion in the previous paragraph considered all cases of nodular Hashimoto thyroiditis in the present study. However, 55% of the cases of nodular Hashimoto thyroiditis in this study occurred within a sonographic background of diffuse Hashimoto thyroiditis, and 45% occurred within normal thyroid parenchyma without any sonographic evidence of diffuse Hashimoto thyroiditis. Thus, nodular Hashimoto thyroiditis occurred with almost equal frequency in the setting of diffuse Hashimoto thyroiditis and in otherwise normal thyroid parenchyma in this study. Note that this result will not necessarily generalize to the entire population because not all the nodules in each patient were biopsied. It is possible that focal abnormalities in an other-

wise normal-appearing thyroid were biopsied more often because the diagnosis of Hashimoto thyroiditis would not be suspected on the basis of the appearance of the thyroid parenchyma. On the other hand, the results could be potentially biased in the other direction, with nodules within a background of diffuse Hashimoto thyroiditis being biopsied more frequently because there is a known increased risk of papillary thyroid cancer and lymphoma in patients with Hashimoto thyroiditis.

When we compared the sonographic features of the nodules within a background of diffuse Hashimoto thyroiditis and those without, nodular Hashimoto thyroiditis coexistent with diffuse Hashimoto thyroiditis was more likely to be solid, to be hyperechoic, to have a thin halo, to lack calcifications, and to occur as a solitary nodule. On the other hand, nodular Hashimoto thyroiditis without coexistent diffuse Hashimoto thyroiditis was more likely to have cystic elements and to have a peripheral eggshell calcification.

Some of these trends are predictable. In patients with diffuse Hashimoto thyroiditis, all nodules should be expected to display a higher echogenicity when compared with the hypoechoic background parenchyma typical of diffuse Hashimoto thyroiditis. This idea may at least partially explain why nodular Hashimoto thyroiditis was more hyperechoic in the setting of diffuse Hashimoto thyroiditis than when it was within an otherwise normal gland. This trend has been noted elsewhere [7]. The heterogeneous nature of diffuse Hashimoto thyroiditis can also make nodules harder to identify and may explain why nodular Hashimoto thyroiditis was more often solitary in the setting of diffuse Hashimoto thyroiditis than in the setting of a normal-appearing background parenchyma.

Compared with previous studies, ours had the advantage of being a large multicenter study. All the ultrasound examinations in our study were performed prospectively, with attention being focused on a predefined group of sonographic features, and the ultrasound images were then reviewed retrospectively in a blinded fashion, whereas the previous studies were completely retrospective [6, 7]. Our study was multicenter to help eliminate any institutional biases, and it had more than double the number of patients with nodular Hashimoto thyroiditis (61 patients with 64 nodules) when compared with the largest of the previous studies [6]. The main objective of our study was to describe the sonographic appearance of nodular Hashimoto thyroiditis, but only one of the previous studies had the same objective [7]. One study focused on the micronodular pattern of diffuse Hashimoto thyroiditis, and, in the process, eight cytologically confirmed cases of nodular Hashimoto thyroiditis were found [2]. Another study focused on assessing the sonographic findings of all thyroid nodules in patients with clinically or pathologically proven diffuse Hashimoto thyroiditis [6].

Nevertheless, our study does have some limitations. One limitation is a selection bias based on the initial decision of whether a nodule should be biopsied. Although Society of Radiologists in Ultrasound guidelines were applied, these guidelines specifically state that recommendations are not absolute or inflexible and that the physician's clinical judgment may justify deferring fine-needle aspiration on nodules that otherwise meet guidelines and that clinical judgment may also justify performing fine-needle aspiration on nodules that do not meet guidelines [8]. Presumably, nodules with low risks of malignancy, according to combined clinical and sonographic features, were less likely to be biopsied than were nodules with higher risks of malignancy. Thus, typically benign features may be underestimated in our statistics, and the nodules in this series may not be entirely representative of all nodular forms of Hashimoto thyroiditis. It is possible that a higher percentage of nodular Hashimoto thyroiditis has features that many regard as benign (> 50% cystic or spongelike). Unless all nodules are biopsied, regardless of risk or sonographic appearance, this type of selection bias is unavoidable. As Tables 1 and 3 illustrate, however, there were many nodules with features traditionally associated with benign nodules that were included in the study. The only type of nodule that was systematically excluded was the purely cystic nodule. In addition, the multiinstitutional nature of the study eliminated the possibility of significant institution-based bias in the selection of nodules that were biopsied.

Another limitation of the present study is that no attempt was made to study the reproducibility of the interpretation of each individual sonographic parameter. We did, however, standardize interpretation among the two readers by starting the analysis with a joint review of 50 cases. We think that this standardization limits the degree to which interobserver variability might affect our results.

In conclusion, the sonographic features and vascularity of nodular Hashimoto thyroiditis were extremely variable and overlapped with the findings typically associated with other benign nodules as well as malignant nodules. We did not find a "typical" sonographic appearance for nodular Hashimoto thyroiditis. In our population of patients who underwent fine-needle aspiration, nodular Hashimoto thyroiditis occurred with nearly equal frequency when diffuse parenchymal changes were present as when the parenchyma was sonographically normal.

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FOR YOUR INFORMATION

The reader's attention is directed to part 2 accompanying this article, titled "Hashimoto Thyroiditis: Part 2, Sonographic Analysis of Benign or Malignant Nodules in Patients With Diffuse Hashimoto Thyroiditis," which begins on page 216.

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