



Long-Term Follow-Up Ultrasonographic Findings of Intrathyroidal Thymus in Children

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Objective: To analyze long-term follow-up sonographic findings of intrathyroidal thymus in children.

Materials and Methods: Among 1259 patients with congenital hypothyroidism under 15 years of age who underwent thyroid ultrasonography (US), 41 patients were diagnosed with an intrathyroidal thymus based on US criteria, i.e., hypoechoic solid lesion with punctate and linear echogenicity. In 26 patients aged one to 14 years old, the last follow-up US was performed after 6 to 132 months and compared with the initial US. The lesion was considered to decrease in size if there was a change of more than 2 mm in any dimension. The margin change was divided into well-defined and indistinct, blurred. When the echogenicity changed to a hyperechoic from a characteristic thymic echogenicity pattern, the pattern was considered a hyperechoic. The changes in size were compared with the changes in shape, margin, and echogenicity pattern. The changes in size, shape, margin, and echogenicity were analyzed the association with the age of last follow-up. Statistical analysis was conducted using the chi-squared test and logistic regression.

Results: Fifteen (57.7%) cases were stable in size, and 11 (42.3%) decreased in size, including one that disappeared. Ten (38.5%) cases changed to indistinct margins from initially well-defined margins including one case of initially indistinct margin. Six (23.1%) changed to hyperechoic, from initially characteristic thymic echogenicity patterns. When follow-up change was compared, decreases in size were significantly associated with lesion changes to indistinct margins ($p = 0.004$). The age at last follow-up was significantly associated with change to hyperechoic (odds ratio, 2.141; 95% confidence interval, 1.144–4.010, $p = 0.017$).

Conclusion: On follow-up US, an intrathyroidal thymus may be decreased in size, with indistinct margins, or show changes to a hyperechoic mass. Decreases in size may be associated with changing to indistinct margins, and changes to hyperechoic may be associated with increasing age.

Keywords: *Intrathyroidal thymus; Pediatrics; US*

INTRODUCTION

Thyroid nodules in children and adolescents are uncommon, with an estimated incidence between 1% and 18% (1). However, the increasing availability of ultrasonographic examinations has resulted in accidental findings of many

more thyroid lesions than previously reported. The risk of cancer in thyroid nodules in children is 22–26%, much higher than the 5–10% risk in adults (2). In accordance with current guidelines, any thyroid lesion found in children, except for pure cysts, requires a thorough diagnostic evaluation, including fine-needle aspiration biopsy (FNAB). In adults, FNAB is routinely recommended as follows: in cases with a high or intermediate suspicion of malignancy, if the nodule size is ≥ 1 cm; in low suspicion cases, if ≥ 1.5 cm; and when the conditions for the spongiform nodule are benign, if ≥ 2 cm (3). Unlike in adults, where lesion size criteria for conducting FNAB exist, in children, a FNAB should be performed even for small but suspicious nodules because children are smaller than adults (2).

The thymus has certain characteristic ultrasonographic features, which include a homogeneous background

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echogenicity similar to that of the liver or spleen, with scattered hyperechoic foci resembling a starry sky (4-10). Ectopic thymic tissue can be located anywhere along the descending path of the thymopharyngeal ducts (5, 11, 12). When ectopic thymic tissue abuts on the inferior or posterior surface of the thyroid or is enclosed by the thyroid parenchyma, the thymus is described as intrathyroidal (4-10). The intrathyroidal thymus has been considered a rare entity, a benign lesion that is unique to the pediatric population and generally requires no treatment (13). The incidence of ectopic intrathyroidal thymus is reported to be between 1% and 5% on screening ultrasonography (US). However, because US has become more frequently used in children, the characteristic features of intrathyroidal thymic tissue used to distinguish it from thyroid nodules have been reported more often, and this intrathyroidal thymus is now more frequently found as a common variant (8, 11-15). Until 2015, 59 cases of ectopic thymic tissue mimicking thyroid nodules or neoplasia detected on US had been published and more cases have been reported since (12, 13, 15-18). The US features of an intrathyroidal thymus are similar to those of a normal thymus. An intrathyroidal thymus may not be recognized by those who are not specialists in pediatric thyroid US, despite its characteristic US appearance. The US appearance of an intrathyroidal thymus can overlap with that of a thyroid nodule. Certain characteristics leading to malignancy suspicion and misdiagnosis have resulted in children undergoing thyroid surgery for suspected malignancy that proved to be benign thymic tissue on surgical pathologic analysis (7, 8, 12-14, 19, 20). A few papers have reported on follow-up US of the intrathyroidal thymus in small numbers of patients (1, 6, 11, 13, 15, 18). The purpose of this study was to analyze the ultrasonographic features of the intrathyroidal thymus mimicking thyroid nodules, upon long-term follow-up, a large number of patients.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board for Ethical Issues in Clinical Research. From January 2006 to December 2017, 1259 patients under 15 years of age who had undergone US for evaluation of congenital hypothyroidism were reviewed retrospectively. Thyroid US was one of the diagnostic protocols for patients diagnosed with congenital hypothyroidism in our hospital and follow-up thyroid US was performed. In this study,

US findings such as aplasia, ectopy, or hemi-aplasia with an undefined thyroid gland in a normal position were excluded. US was performed by a pediatric radiologist or by residents under the supervision of the same pediatric radiologist. The US examinations were conducted using a 5–18 MHz high-frequency linear transducer or a hockey stick probe on one of two US scanners (IU 22, Philips Healthcare; or GE Logiq E9, GE Healthcare). A solid thyroid mass was seen in 52 lesions of 52 patients with a normally positioned thyroid gland. An intrathyroidal thymus was considered to be diagnosed when a hypoechoic lesion with punctate and linear echogenicity was observed. Areas of ectopic extrathyroidal tissue connected to the mediastinal thymus were not included in this study. Eleven patients were excluded because they did not have any US criteria characteristic of intrathyroidal thymus. If an image was available, the lesions were compared with the mediastinal thymus. Forty-one patients were diagnosed with an intrathyroidal thymus based on the US criteria from the previous reports (Fig. 1). All patients were diagnosed using US features. Patient characteristics, including age and sex and US features, including size, site, location, shape or margin were analyzed. The locations were classified as belonging to the superior, middle or inferior portion of the thyroid gland, on longitudinal scans. A lesion abutting the superior border of the thyroid was considered superior, one abutting the inferior border was considered inferior, and the others were considered as belonging to the middle portion

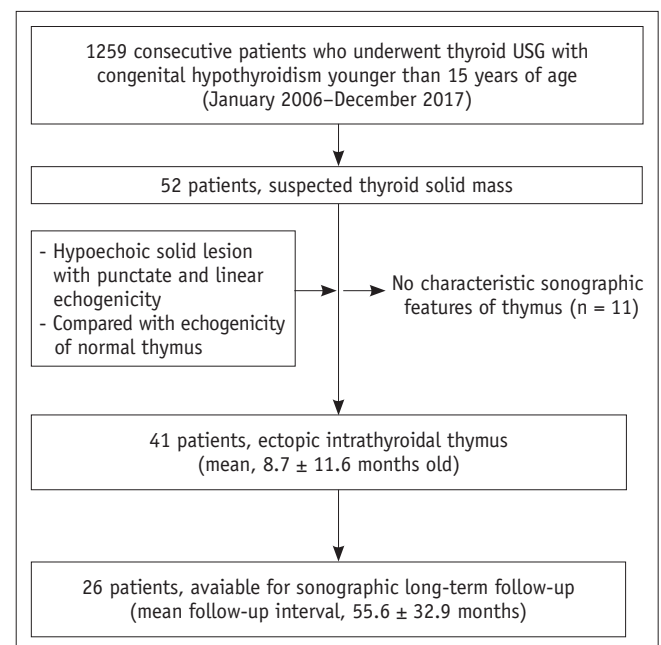


Fig. 1. Flow chart of study.

of the thyroid gland. On transverse scans, the locations of the lesion were divided into anterior, center and posterior, depending on whether the lesions abutted the anterior or posterior border or neither. The lesion size measured on the transverse and longitudinal scans was recorded and the largest diameter among them was considered the maximum diameter of the lesion. The shape was classified as oval, round, or irregular. The margins were divided into well-defined and indistinct/blurred.

Follow-up US was available for 26 patients and the last follow-up US was performed within a range of 6 to 132 months (mean, 55.6 ± 32.9 months). The age at the last follow-up US was between 1 and 14 years. The findings from the last follow-up US were reviewed and compared with the initial US for size, shape, margin, and echogenicity pattern features. When changes of more than 2 mm in any dimension were found between the initial and the last follow-up US evaluation, the lesion was considered to have decreased in size. The margin changes were divided into two types: well-defined and indistinct/blurred. When the echogenicity changed to a hyperechoic, from the characteristic thymic echogenicity pattern, the pattern was considered hyperechoic. The changes in size on follow-up US were compared to the changes in shape, margin, and echogenicity pattern. The changes in size, shape, margin, and echogenicity pattern were analyzed for associations with the age of the last follow-up US. Statistical analysis was performed with SPSS 20.0 (IBM Corp.) using chi-squared tests and binary logistic regression analysis. A difference was considered statistically significant for a *p*-value of less than 0.05.

RESULTS

An intrathyroidal thymus was found in 3.3% (41/1259) of patients, of which 24 were male and 17 female, with a mean age of 8.7 ± 11.6 months (range, one week to 3 years 10 months). The mean maximum diameter was 7.3 ± 5.3 mm (range, 3 to 25 mm). We were able to compare the scans of 31 patients who had scans of a mediastinal thymus. Twenty-two (53.7%) patients had lesions on the right, and 19 (46.3%) had lesions on the left. The intrathyroidal thymus was mostly located in the middle portion of the thyroid lobe (33/41, 80.5%) and, less frequently, in the inferior portion (8/41, 19.5%). No lesions were located in the superior portion on longitudinal scans. There were 24 (58.5%) lesions in the center of the gland and 17 (41.5%) in the

posterior portion on transverse scans. The lesions were oval in 14 cases (34.1%), round in 23 (56.1%), and irregular in four (9.8%). The margins of the lesions were well-defined in 40 (97.6%) cases and indistinct or blurred in one (2.4%) (Table 1).

During the follow-up period, 15 (57.7%, 15/26) lesions were stable in size, and 11 (42.3%, 11/26) lesions decreased in size, including one that disappeared. Ten (38.5%, 10/26) lesions had changed to indistinct, blurred margins from initially well-defined margins (Figs. 2, 3). One case of an initially indistinct margin also included indistinct, blurred margins. Six (23.1%, 6/26) lesions changed to hyperechoic patterns from the initial characteristic thymic echogenicity patterns (Figs. 4, 5). When the follow-up size was compared to the changes in shape, margin, or echogenicity pattern, a statistically significant difference was seen between the size and the margin. Decreases in size were significantly associated with changes to indistinct or blurred margins ($p = 0.004$) (Table 2). However, no statistical associations were found between decreases in size and changes in shape or to hyperechoic pattern. The last follow-up age was significantly associated with changes to hyperechoic patterns (odds ratio [OR], 2.141; 95% confidence interval [CI], 1.144–4.010; $p = 0.017$) (Fig. 5). However, other changes in size, shape, or margin type were not significantly associated with the age at the last follow-up (Table 3).

Table 1. Lesion Analysis of Intrathyroidal Thymus

	Total	Right Lobe	Left Lobe
Longitudinal scan			
Superior	0 (0)	0 (0)	0 (0)
Middle	33 (80.5)	15 (36.6)	18 (43.9)
Inferior	8 (19.5)	7 (17.1)	1 (2.4)
Transverse scan			
Anterior	0 (0)	0 (0)	0 (0)
Center	24 (58.5)	11 (26.8)	13 (31.7)
Posterior	17 (41.5)	11 (26.8)	6 (14.6)
Shape			
Oval	14 (34.1)	7 (17.1)	7 (17.1)
Round	23 (56.1)	12 (29.3)	11 (26.8)
Irregular	4 (9.8)	3 (7.3)	1 (2.4)
Margin			
Well-defined	40 (97.6)	21 (51.2)	19 (46.3)
Indistinct/Blurred	1 (2.4)	1 (2.4)	0 (0)
Total	41 (100)	22 (53.7)	19 (46.3)

Values are presented as n (%) unless otherwise indicated.

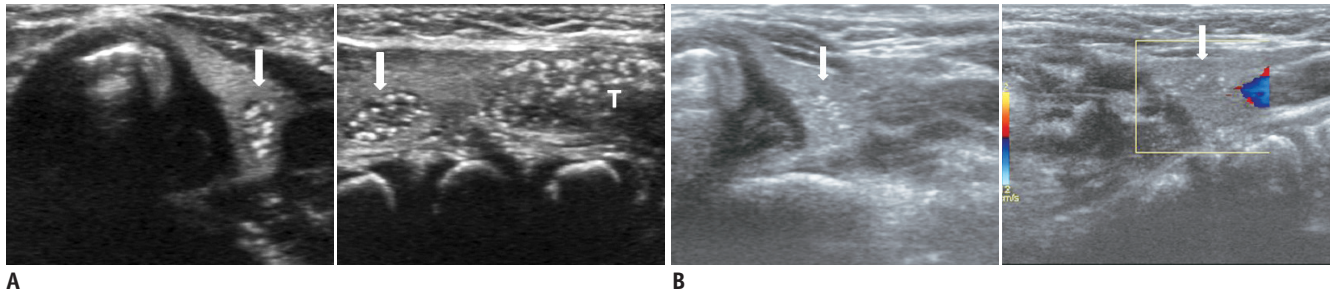


Fig. 2. 1-year-old girl with intrathyroidal thymus.

A. Transverse and longitudinal US scans show 7 mm intrathyroidal thymus (arrow) in center and middle portion of left thyroid gland with same echogenicity pattern as mediastinal thymus (T). **B.** Follow-up transverse and longitudinal scans at age of 3 years show that diameter of lesion decreased more than 2 mm in size and thymic echogenicity pattern did not change, but margin did change to indistinct from well-defined (arrow).

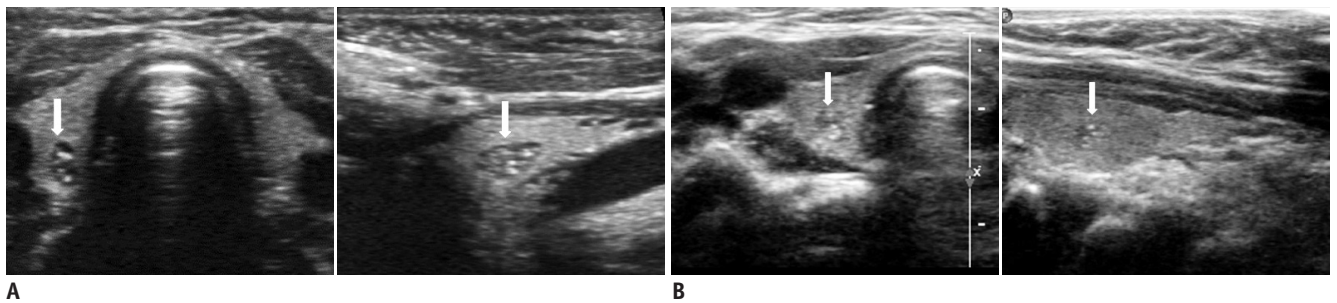


Fig. 3. 7-month-old boy with intrathyroidal thymus.

A. Transverse and longitudinal US scans show 5 mm intrathyroidal thymus (arrow) in center and middle portion of right thyroid gland. **B.** At 3-year follow-up, transverse and longitudinal scans show intrathyroidal thymus more than 2 mm smaller in diameter with change to indistinct margin. There was no change in thymic echogenicity pattern (arrow).

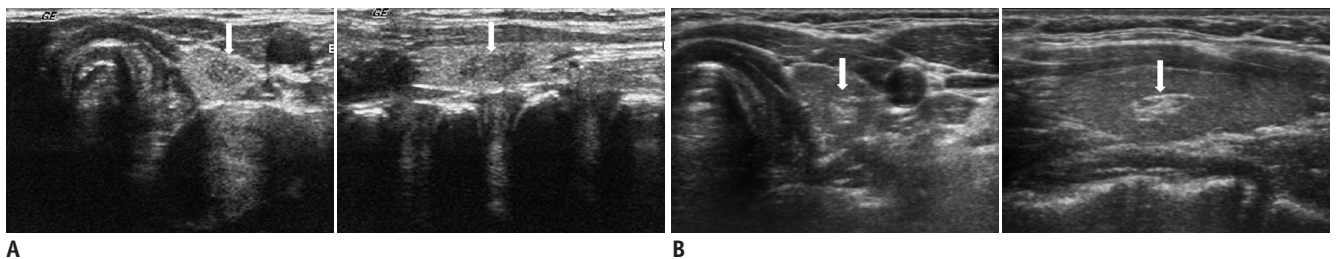


Fig. 4. 3-year-old boy with intrathyroidal thymus.

A. Transverse and longitudinal US scans show 7 mm intrathyroidal thymus (arrow) in center and middle portions of left thyroid gland. **B.** Follow-up transverse and longitudinal scans at 14-years show that lesion did not change in size and had well-defined margin. However, echogenicity pattern changed to hyperechogenic (arrow).

DISCUSSION

Some studies have confirmed that the presence of an intrathyroidal thymus through cytology or surgery due to the fear that children with suspicious thyroid lesions are misdiagnosed (4, 5, 12, 13, 15, 16, 21, 22). However, a few studies on the ultrasound characteristics and the prevalence of intrathyroidal thymus were based on US images only, without cytological evaluation, and suggested that US could be used as a common diagnostic tool to identify a benign intrathyroidal thymus (11, 13, 17, 23). In addition, awareness of the characteristic features of an intrathyroidal

thymus and how they differ from the malignant finding and of the follow-up changes will be helpful for accurately diagnosing patients and determining the next procedures to be performed.

In previously reported studies investigating intrathyroidal thymus follow-up, an initial US was performed in 9 to 22 patients aged of 2.5 weeks to 17.5 years. In these studies, follow-up US was performed in 1 to 13 patients, at interval ranging from 6 to 84 months (mean, 30.7 months) (1, 6, 11, 13, 15, 18). In our study, we analyzed the initial US findings of 41 patients with an average age of 8.7 months, with an intrathyroidal thymus. Follow-up US was performed

in 26 patients, at an interval of up to 132 months (mean, 55.6 months). To the best of our knowledge, this is the first study analyzing long-term US follow-up on intrathyroidal thymus cases, in the largest number of patients.

The most important clues for an accurate differential diagnosis between an intrathyroidal thymus and thyroid nodules are the presence of a fusiform shape and well-defined margins and a characteristic hypoechoic solid

mass with bright internal punctate or linear echogenicity, similar to the normally descended thymus (4, 5, 11, 16). In our study, most lesions were round and small (less than 10 mm) or oval in shape. Except for one, most lesions had well-defined margins. All cases of intrathyroidal thymus had US patterns similar to those of a normal thymus in the mediastinum.

Thymic involution is defined as the process in which the gland decreases in size and weight with advancing age (24). The process of age-related thymic involution remains poorly understood despite many reports examining age-related changes in thymic physiology (25). The thymus has the greatest relative size at birth and continues to grow until it reaches its greatest absolute size at puberty (11). Because the incidence of intrathyroidal thymus is inversely correlated with age, the intrathyroidal thymus would be expected to follow the same growth trends as normal thymic tissue, as they are derived from the same tissue (11, 23). Several follow-up studies reported that most lesions remained stable and some lesions shrank (6, 11, 13, 18). Segni et al. (6) reported that normal thymus involution occurs with advancing age, in patients aged 13 and 17 years. However, another study reported that thymus regression in puberty may occur earlier than previously reported, as smaller changes were observed at five or six years of age. It was also reported that many lesions were stable and no changes in shape, border, or echotextures were observed on follow-up imaging analysis (11, 13). Kabaalioglu et al. (11) reported that one patient with an intrathyroidal thymus, diagnosed by FNAB, showed an increase in echogenicity and a less well-defined border in a follow-up at age five. These changes to increasing echogenicity and less well-defined borders have been observed during the involution phase of the thymus (6, 11). In our study, a decrease in lesion size was seen in 42.3% (11/26) of the patients. One lesion had disappeared in a 3-year-old at the follow-up, which is too young of an age to have coincided with thymic involution. On follow-up, the decrease in the size of the lesion was

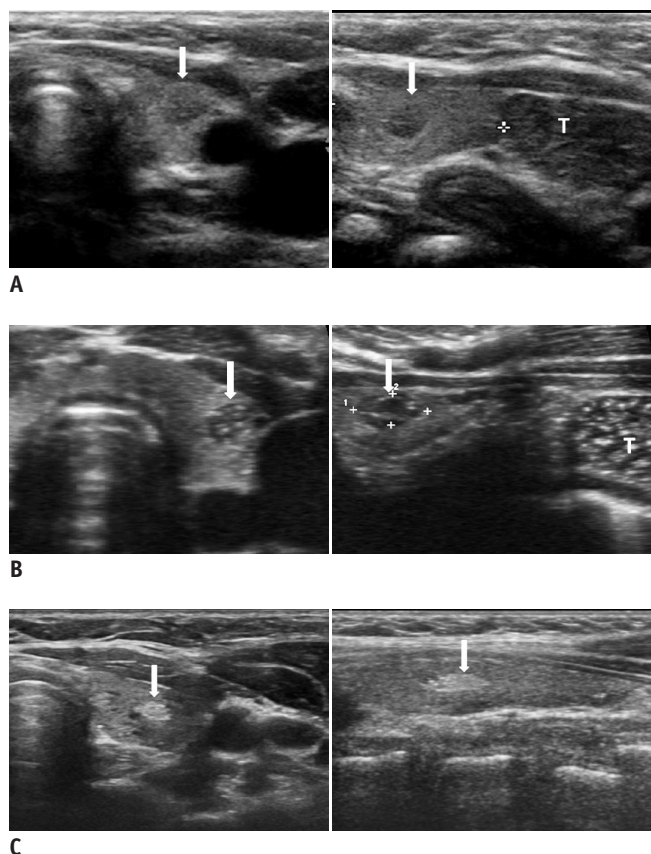


Fig. 5. Serial follow-up images of intrathyroidal thymus.
A. 3-month-old boy had round, well-defined intrathyroidal thymus (arrow) in left thyroid gland with same echogenicity pattern as mediastinal thymus (T). **B.** Follow-up image at age of 1 year shows no significant change in size, margin or echogenicity patterns (arrow). **C.** Follow-up scan at 8 years shows that lesion had changed to hyperechoic pattern without significant changes in size or margins (arrow).

Table 2. Comparison of Follow-Up Size, Shape, Margin, and Echogenicity Patterns

	Total	Shape			P	Margin		P	Echogenicity Pattern		P
		Oval	Round	Irregular		Well-Defined	Indistinct/Blurred		Isoechogenicity [†]	Hyperechogenicity	
Size					0.310			0.004			0.197
Stable	15 (57.7)	5 (19.2)	6 (23.1)	4 (15.4)		13 (50.0)	2 (7.7)		10 (38.5)	5 (19.2)	
Smaller	11 (42.3)	3 (11.5)	2 (7.7)	6 (23.1)* [†]		3 (11.5)	8 (30.8)* [†]		10 (38.5)* [†]	1 (3.8)	
Total	26 (100)	8 (30.8)	8 (30.8)	10 (38.4)		16 (61.5)	10 (38.5)		20 (76.9)	6 (23.1)	

Values are presented as n (%) unless otherwise indicated. *Disappeared one patient, [†]Initially indistinct, blurred margin one patient, [‡]Similar echogenicity to that of thymus

Table 3. Logistic Regression Analysis of Last Follow-Up Age with Size, Shape, Margin, and Echogenicity Patterns

Features at Last Follow-Up		β (SE)	Odds Ratio	95% Confidence Interval	P
Size	No change	-0.032 (0.126)	0.968	0.756–1.240	0.799
	Decreased or disappeared				
Shape	Oval, round	0.020 (0.126)	1.020	0.796–1.306	0.876
	Irregular				
Margin	Well-defined	-0.045 (0.130)	0.956	0.741–1.232	0.726
	Indistinct/Blurred				
Echogenicity pattern	Isoechogenicity*	0.761 (0.320)	2.141	1.114–4.010	0.017
	Hyperechogenicity				

*Similar echogenicity to that of thymus. SE = standard error

significantly associated with changes to blurred margins. However, one patient with a margin which was not well-defined on the initial US was aged two. This could pose a problem in the achieving an accurate differential diagnosis from a malignant thyroid nodule. Knowing that a decrease in intrathyroidal thymus size could be associated with a change to a blurred margin can help in recognizing an incidentally found intrathyroidal thymus and provide information for a correct differential diagnosis from a malignant thyroid nodule in children. In our study, hyperechoic changes from the thymic echogenicity pattern were significantly associated with the last follow-up age and this could represent the thymic involution process of fatty replacement. The US internal echogenicity of the intrathyroidal thymus is known to correspond to fat or connective tissue septa and vessels in the thymic tissue (11, 16). During the involution phase, the atrophy of the epithelial component results in a fatty replacement of the cellular components of the thymus and may induce a hyperechoic change from the normal thymic echogenicity pattern.

US features suggestive of malignant thyroid nodules include the presence of microcalcifications, irregular margins, taller than wide dimensions, hypoechoic solid nodules, increased vascularity, and abnormal lymph nodes (9, 16, 26). Children with hypoechoic nodules with microcalcification-like echogenicity are often referred for biopsy or surgery due to a strong suspicion of malignancy (11, 13, 17, 23). The diffuse sclerosing variant of papillary thyroid carcinoma tends to have a diffuse pattern of microcalcifications imparting a snowstorm appearance on ultrasound. It also tends to be more commonly reported in young patients, while being associated with a worse prognosis than conventional papillary carcinoma (16, 27). Punctate bright internal echogenicity in the intrathyroidal thymus are most commonly confused with microcalcifications, such as the diffuse sclerosing variant of

papillary carcinoma, which can truly mimic thymic tissue on US. To avoid a missed or delayed diagnosis, clinicians may prompt referral to US-guided FNAB (16).

Although there is considerable overlap between the ultrasound findings of benign and malignant thyroid nodules, knowledge of the typical ultrasound features of an intrathyroidal thymus can help with differentiating it from other thyroid lesions and assist in making a definite diagnosis based on ultrasound. In addition, there is limited age overlap between the patients with an intrathyroidal thymus and those with thyroid malignancies, because the prevalence of thyroid malignancies increases with age and the intrathyroidal thymus spontaneously involutes in late childhood (16). At follow-up, most of our patients did not show any problems or complications related to an intrathyroidal thymus. Therefore, if an incidentally found thyroid nodule in children displays the characteristic US appearance of an intrathyroidal thymus that can be compared with a normal mediastinal thymus, additional evaluation may not be necessary. However, in some phase of involution, the intrathyroidal thymus could have certain characteristics, such as an indistinct margin, irregular appearance, or internal echogenicity mimicking microcalcifications that are similar to those of thyroid malignancies. If the other US lesion findings lead to a suspicion for an intrathyroidal thymus, but there is, in young children, an indistinct margin, irregular appearance, or internal echogenicity mimicking microcalcifications, regular follow-up US may be recommended until the intrathyroidal thymus decreases in size or changes to hyperechoic patterns in order to differentiate it from malignancy. However, if these US findings were seen in older children or adolescents, US-guided FNAB should be recommended to the patient. Distinguishing suspicious thyroid nodules from an intrathyroidal thymus using US requires a great deal of experience with the intrathyroidal thymus. Thus,

if the radiologist or the clinician is knowledgeable in the benign characteristics of the intrathyroidal thymus and its long-term changes, patients can avoid further unnecessary invasive procedures such as FNAB or surgery (13).

There were several limitations to our study. First, it was a retrospective review of thyroid US and the incidence of intrathyroidal thymus may have been underestimated. Second, all patients were diagnosed by US findings and none of them had a pathologic diagnosis. Therefore, the possibility of misdiagnosis cannot be excluded. Third, many of the intrathyroidal thymus had subcentimeter sizes of less than 10 mm and comparing changes in small lesions may not be accurate. Fourth, the follow-up age distribution was not even and only two patients were available at follow-up ages of over 10 years old. Finally, because the lesions are expected to disappear following puberty, we were not able to observe regression in all our patients.

In conclusion, an intrathyroidal thymus appears as a round or oval, circumscribed, hypoechoic mass with the characteristic echogenicity features of the thymus. On follow-up US, an intrathyroidal thymus may be decreased in size, with indistinct or blurred margins, or changed to a hyperechoic mass. Decreases in size may be associated with changes to indistinct margins. A change to a hyperechoic pattern in the intrathyroidal thymus may be associated with increasing age. Awareness of the characteristic US features and follow-up changes in an intrathyroidal thymus in children is important to avoid misdiagnosing it as a malignant nodule and unnecessary interventional procedures or surgery.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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