Original Article

AUTONOMOUSLY FUNCTIONING THYROID NODULES IN PATIENTS <21 YEARS OF AGE: THE RHODE ISLAND HOSPITAL EXPERIENCE FROM 2003-2013

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ABSTRACT

Objective: This study evaluates the clinical characteristics, workup, treatment, and outcomes of pediatric patients diagnosed with an autonomously functioning thyroid nodule (AFTN) in a large cohort of patients presenting for evaluation of a thyroid nodule. There are few prior studies on AFTN in pediatrics, with limited data on treatment and outcomes. Rates of malignancy in AFTN are perceived as low, but prior studies have varying reports.

Methods: This is a retrospective chart review of patients less than 21 years of age at Rhode Island Hospital over an 11-year period (2003-2013). We reviewed 354 charts, which yielded 242 patients with a diagnosis of thyroid nodule and 17 patients with AFTN.

Results: The prevalence of AFTN in patients presenting with thyroid nodules was 7%. Mean age of patients was 15.8 years at diagnosis, and mean nodule size was 3.3 cm. There was female predominance. Thyroid-stimulating hormone levels were suppressed at diagnosis in 87% of patients. Six patients were treated with surgery, 5 patients with radioactive iodine therapy (RAI), 2 patients with medication, and 1 patient was observed without treatment. Three patients treated with RAI required subsequent treatment for hypothyroidism or continued hyperthyroidism. One patient had papillary thyroid carcinoma based on final surgical pathology.

Conclusion: Our study found a higher prevalence of AFTN compared to the reported prevalence in adults. We concur with the new guidelines on management of thyroid nodules in recommending surgery for treatment of AFTN, based on the variability of outcomes after treatment with RAI. **(Endocr Pract. 2016;22:328-337)**

Abbreviations:
AFTN = autonomously functioning thyroid nodule; **anti-TG** = thyroglobulin antibodies; **anti-TPO** = thyroid peroxidase antibodies; **FNA** = fine-needle aspiration; **ICD-9** = International Classification of Diseases, Ninth Revision; **PTC** = papillary thyroid carcinoma; **RAI** = radioactive iodine; **T_3** = triiodothyronine; **T_4** = thyroxine; **TSH** = thyroid-stimulating hormone; **TSI** = thyroid-stimulating immunoglobulin

INTRODUCTION

There are few studies on autonomously functioning thyroid nodules (AFTNs) in pediatrics. Previous studies have a small number of patients and minimal data on treatment and follow-up (1-4). AFTN in adults has been reported as 5% of all thyroid nodules (5). There are limited data in children due to the few number of studies, but in the studies available, AFTN has been reported in 5 to 7.5% of pediatric patients presenting with thyroid nodules (1,6,7).

Malignancy is the most concerning diagnosis when a patient presents with a thyroid nodule. Cold thyroid nodules are thought to have a higher risk for malignancy compared to AFTN. Studies show malignancy is present in cold nodules in pediatric patients with a range of 9 to 50%, averaging 26.4% (8). Although malignancy is thought to be rare in AFTN, there are some case reports of malignancy in AFTN in pediatrics (9). In the few studies available, the

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rate of malignancy in AFTN ranges from 0 to 29% (1-4,10). Here, we report the demographic data, laboratory findings, imaging results, histologic findings, treatment data, and outcomes for patients found to have AFTN who were less than 21 years of age at diagnosis, over an 11-year period. This period is prior to the publication of new guidelines on management of thyroid nodules in pediatrics from the American Thyroid Association (11). These guidelines published in 2015 provide recommendations for the evaluation and treatment of thyroid nodules and differentiated thyroid cancers in pediatrics and includes recommendations for the evaluation and treatment of AFTN as well. In light of these new guidelines, we aim to compare our management practices in the recent years to the recommendations in the new guidelines.

METHODS

This is a retrospective chart review of patients less than 21 years of age at Rhode Island Hospital from 2003-2013. We searched all patients seen at Rhode Island Hospital and Hasbro Children's Hospital who were less than 21 years of age and had the International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code for thyroid nodule (ICD-9 code 241). We also searched the ICD-9 diagnosis code for autonomously functioning thyroid nodule (ICD-9 code 242.1) during this same time period. We reviewed those patients that were seen between January 2003 and December 2013. Clinical notes, laboratory results, imaging results, and pathology results were analyzed for these patients to determine the final diagnoses.

There were 354 patients with the diagnosis code for thyroid nodule. We reviewed the charts to verify the diagnosis of thyroid nodule, which was confirmed by a thyroid nodule seen on ultrasound. A total of 112 patients had incorrect diagnosis codes. Many of these patients had a thyroid nodule on exam but had a thyroid ultrasound that showed no evidence of a thyroid nodule. A total of 242 patients were found to have a thyroid nodule confirmed by ultrasound. Patients were separated into categories based on the final diagnoses. These results are detailed in Figure 1. There were only 2 patients found when searching the ICD-9 code for AFTN. Both of these patients also had the ICD-9 code for thyroid nodule and were included in the initial review of patients presenting with a thyroid nodule.

Diagnosis of AFTN was based on presence of a thyroid nodule on ultrasound and a low thyroid-stimulating hormone (TSH) laboratory result, or AFTN visualized on thyroid uptake scan. AFTN was diagnosed on thyroid uptake scan if a focal area of increased uptake was documented in the radiology report written by experienced radiologists. Many patients also had suppression of the surrounding thyroid tissue, but this was not a criterion for diagnosis of an AFTN. Patients with single and multiple nodules were included in this study. Demographic data, laboratory results, imaging results, pathology results, treatment modalities, and outcomes of the patients with the diagnosis of AFTN are detailed in this paper. The Rhode Island Hospital Institutional Review Board approved this study.

RESULTS

Of all pediatric patients presenting with a thyroid nodule, the most common diagnosis was a benign nodule in 72 of 242 patients (29.8%), as shown by a benign fine-needle

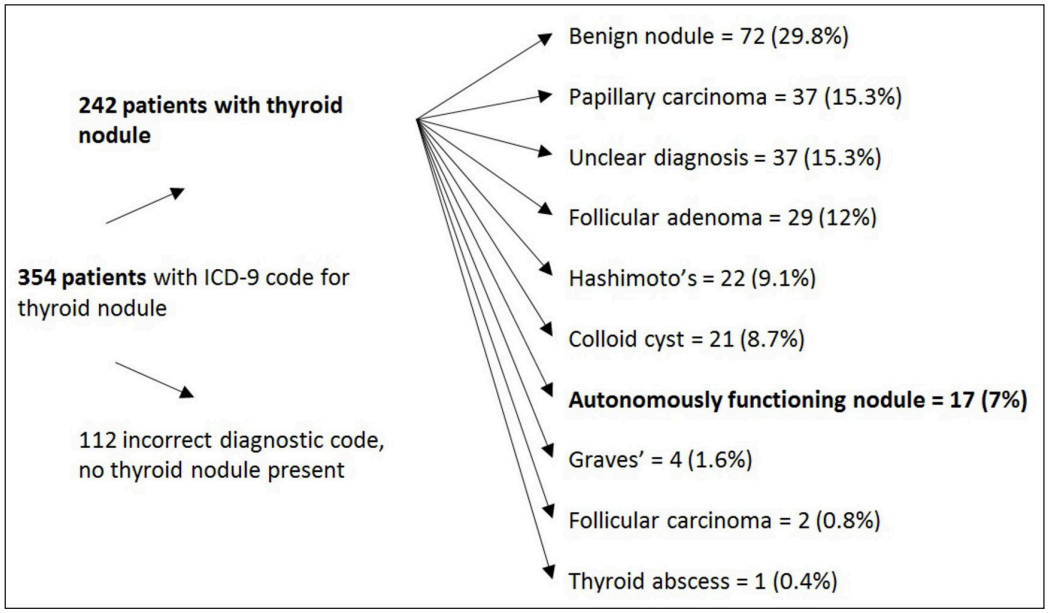

Fig. 1. Flowchart of chart review findings.

aspiration (FNA) or by resolution of the nodule over time without intervention. The second most common diagnosis was papillary thyroid carcinoma (PTC) in 37 of 242 patients (15.3%). AFTN was present in 17 of 242 patients presenting for thyroid nodule, with a prevalence of 7%. The full range of diagnoses is detailed in Figure 1.

Clinical Characteristics

The median age at diagnosis of patients with AFTN was 17 years (range, 5 to 19.8 years). There was female predominance, with 15 females and 2 males. Five patients had nodules discovered by healthcare providers; 3 patients presented with symptoms of hyperthyroidism; 3 patients had nodules found incidentally on imaging; 2 patients had nodules detected by family members; 1 patient was followed for Graves disease and was found to have a thyroid nodule; 3 patients did not have presentation data available. Eight patients had symptoms associated with hyperthyroidism at diagnosis, whereas 4 patients were completely asymptomatic, and 2 patients only had symptoms of throat tightness or difficulty swallowing. The median nodule size was 3.5 cm (range, 2.2 to 4.7 cm), based on measurements reported in the initial ultrasound done to evaluate the thyroid nodule. Laterality of AFTN was 9 right, 3 left, 3 bilateral, and 2 isthmus, as reported by ultrasound and thyroid uptake scan findings. Demographic data, nodule size, and clinical presentation for each individual patient are detailed in Table 1.

Biochemical Studies

Thyroid function studies at the time of diagnosis were available for 15 of the 17 patients with AFTN. Laboratory results were all collected and processed at Lifespan Laboratories. TSH levels were suppressed at diagnosis in 87% of patients, with median value 0.03 μIU/mL and range 0.008 to 0.95 μIU/mL (normal values, 0.35 to 5.50 μIU/mL). Total thyroxine (T_4) levels were elevated in 45% of patients, with a median value of 10.9 μg/dL and range 5.7 to 19.1 μg/dL (normal values, 4.5 to 10.9 μg/dL), and free T_4 levels were elevated in 11% of patients, with a median value of 1.16 ng/dL and range 0.92 to 1.83 ng/dL (normal values, 0.8 to 1.8 ng/dL). Total triiodothyronine (T_3) levels were elevated in 73% of patients, with a median value of 228 ng/dL and range 78 to 522 ng/dL (normal values, 80 to 210 ng/dL), and free T_3 levels were elevated in 17% of patients, with a median value of 360.7 pg/dL and range 326.7 to 450.5 pg/dL (normal values, 230 to 420 pg/dL). Thyroid antibodies, including thyroid-stimulating immunoglobulin (TSI), thyroid peroxidase antibodies (anti-TPO), and/or thyroglobulin antibodies (anti-TG) were measured in 12 of 17 patients, and 3 of these patients (25%) had 1 or more elevated antibody level. As detailed in Table 2, patient 6 had an elevated anti-TG, patient 14 had a slightly elevated TSI and an elevated anti-TG with a normal anti-TPO, and patient 15 had a very elevated TSI and was known to have Graves disease with a superimposed AFTN. Laboratory values, including thyroid function studies and thyroid autoantibody results, are detailed in Table 2.

Radiographic Studies and FNA Results

Thyroid uptake scan was done in 14 of 17 patients, and all showed a focus of increased uptake consistent with an AFTN. There was variability in the suppression of activity in the remainder of the lobe, with these results detailed in Table 3. Thyroid uptake scan showed an elevated 24-hour uptake in 5 of 14 patients (36%). Figure 2 shows the thyroid uptake scan for patient 9, who had a 3.8-cm left-sided AFTN. Thirteen patients had an FNA as part of the evaluation for AFTN. Twelve of these patients had benign cytology results from the FNA, and 1 patient had cytology that was suggestive of a follicular neoplasm. Thyroid uptake scan results and FNA results are detailed in Table 3.

Treatment and Follow-up

Six patients were treated with surgery, 5 patients with radioactive iodine (RAI) therapy, 2 patients with medication, 1 patient was observed without treatment, and 3 patients had no treatment information available. Of the patients that underwent surgery, final pathology showed adenomatous nodules in 4 patients, a hyperplastic nodule with focal lymphocytic thyroiditis in 1 patient, and PTC in 1 patient. Interestingly, the patient with PTC had benign FNA cytology results. Due to findings on ultrasound that were suspicious for malignancy, hemi-thyroidectomy was done and PTC was found on final pathology. Of the 6 patients treated with hemi-thyroidectomy, 2 patients subsequently had a total thyroidectomy (1 for PTC and 1 for development of further nodules) and required thyroid replacement with levothyroxine, 2 patients had normal thyroid function tests and did not require further treatment (followed for 1.8 and 2.4 years after treatment), and 2 patients did not have follow-up data available. Of the 5 patients that were treated with RAI, 2 patients developed hypothyroidism (1.1 years and 3.4 years after treatment), 1 patient who also had Graves disease continued to have subclinical hyperthyroidism 1 year after RAI that was treated with methimazole, and 2 patients had normal thyroid function tests and did not require further treatment (followed for 0.2 years and 2 years after treatment). Treatment and follow-up data for each patient are detailed in Table 3.

DISCUSSION

Our study found a slightly higher prevalence of AFTN in pediatric patients presenting with a thyroid nodule compared to the reported prevalence in adults (5). The majority of patients were diagnosed in adolescence, with only 2 patients diagnosed before 11 years of age. There was 1 patient in our cohort who was found to have cancer in

Table 1
Age, Sex, Nodule Size, Laterality, and Presentation of Each Patient with an AFTN

Patient	Sex	Age[a] (years)	Nodule size[b] (cm)	Laterality	Presentation[c]	Thyroid symptoms present at diagnosis
1	F	5	2.7	L	Nodule found incidentally on MRI spine for scoliosis	None
2	F	10.5	2.2	R	Neck mass noticed by mother	None
3	F	13.7	4.7	R	Symptoms of hyperthyroidism	Heat intolerance, anxiety
4	F	13.7	3.5	Bilateral	Nodule found on US after an episode of fever and thyromegaly	Difficulty swallowing
5	F	13.9	3.9	R	N/A	N/A
6	M	14.4	3.8	R	Nodule found by primary care physician on routine exam	Insomnia, alternating diarrhea and constipation
7	F	15.3	3	Isthmus	Nodule found by psychiatrist after presentation with depression and behavioral issues	Heat intolerance, insomnia, headache, decreased concentration
8	F	16.3	3.9	R	Neck mass noticed by mother	Heat intolerance, headaches, increased appetite
9	F	17	3.8	L	Nodule found incidentally on MRI spine for scoliosis	Throat tightness
10	F	17.4	3.5	Bilateral	Symptoms of hyperthyroidism	Palpitations, weight loss, fatigue, difficulty swallowing
11	F	17.5	2.8	Bilateral	Referred to endocrine for abnormal TFTs, nodule found on exam by endocrinologist	None
12	F	17.8	N/A	L	N/A	N/A
13	F	18.4	N/A	R	N/A	N/A
14	F	19.2	3.1	R	Symptoms of hyperthyroidism	Hot flashes, headaches, visual hallucinations
15	M	19.7	3	R	Graves disease with superimposed nodule	Increased appetite
16	F	19.7	3.6	R	TFTs showed thyrotoxicosis, referred to endocrine and found to have thyroid nodule on exam	Amenorrhea, anxiety
17	F	19.8	2.4	Isthmus	Nodule noted incidentally at school nurse visit	None
Mean		15.8	3.3			
Median		17	3.5			
Range		5-19.8	2.2-4.7			

Abbreviations: AFTN = autonomously functioning thyroid nodule; F = female; L = left; M = male; MRI = magnetic resonance imaging; N/A = not available; R = right; TFT = thyroid function test; US = ultrasound.
[a] Age represents the age in years at initial diagnosis of AFTN.
[b] Nodule size is the measured size from the ultrasound report at diagnosis.
[c] Presentation as documented in outpatient medical records.

Table 2
Laboratory Results of Each Patient with an AFTN at Time of Diagnosis

Patient	TSH (0.35-5.50 μIU/mL)	Total T_4 (4.5-10.9 μg/dL)	Free T_4 (0.8-1.8 ng/dL)	Total T_3 (80-210 ng/dL)	Free T_3 (230-420 pg/dL)	Antibodies[a]
1	0.008	10.9	N/A	269	N/A	Negative TSI, anti-TPO, anti-TG
2	0.096	7.5	N/A	N/A	N/A	Negative TSI, anti-TPO, anti-TG
3	0.009	19.1	N/A	522	N/A	Negative TSI, anti-TPO
4	0.04	8.1	N/A	226	N/A	Negative TSI, anti-TPO, anti-TG
5	<0.03	N/A	1.83	N/A	N/A	N/A
6	0.015	12.9	N/A	295	N/A	Anti-TG elevated (8 IU/mL, normal <2 IU/mL). TSI and anti-TPO not done
7	0.15	5.7	1.1	161	326.7	Negative TSI, anti-TPO, anti-TG
8	<0.03	10.1	N/A	200	N/A	Negative TSI, anti-TPO, anti-TG
9	0.008	8.8	1.21	220	450.5	Negative anti-TPO, anti-TG. TSI not done
10	<0.03	N/A	1.18	260	N/A	Negative TSI, anti-TG. Anti-TPO not done
11	0.41	11	1.09	228	N/A	Negative anti-TPO, anti-TG. TSI not done
12	N/A	N/A	N/A	N/A	N/A	N/A
13	N/A	N/A	N/A	N/A	N/A	N/A
14	0.108	16.2	1.16	301	351.1	Negative anti-TPO. TSI slightly elevated (126%, normal <125%). Anti-TG elevated (70.4 U/mL, normal <60 U/mL)
15	0.141	11.1	1.62	148	379.7	Elevated TSI (620%, normal <125%)
16	0.008	N/A	0.92	N/A	349.6	N/A
17	0.95	N/A	0.96	N/A	370.2	N/A
Mean	0.136	11.0	1.23	257	362.7	
Median	0.03	10.9	1.16	228	360.7	
Range	0.008-0.95	5.7-19.1	0.92-1.83	78-522	326.7-450.5	

Abbreviations: AFTN = autonomously functioning thyroid nodule; anti-TG = thyroglobulin antibodies; anti-TPO = thyroid peroxidase antibodies; N/A = not available; T_3 = triiodothyronine; T_4 = thyroxine; TSH = thyroid-stimulating hormone; TSI = thyroid-stimulating immunoglobulin.

[a] TSI, negative <125% or <140%, depending on the assay; anti-TPO, negative <2 IU/mL or <60 IU/mL, depending on the assay; anti-TG, negative <2 IU/mL or <60 IU/mL, depending on the assay.

Table 3
Thyroid Uptake Scan Results, FNA Results, Treatment, and Follow-Up Data of Each Patient With an AFTN

Patient	Thyroid uptake scan results	24-hour uptake (10-35%)	FNA results	Treatment	Follow-up
1	Intense focus of increased uptake in the left lobe with suppression of the rest of the thyroid, consistent with an AFTN	28.2%	Benign	Methimazole	Continues on methimazole, labs monitored 3-4 times a year with fluctuation of TSH, US done every 1-3 years with some increase in nodule size to 3.8 cm over 10 years
2	Not done	N/A	Benign	Lobectomy, final pathology **papillary thyroid carcinoma**, total thyroidectomy done	Started levothyroxine immediately after completion thyroidectomy
3	Enlarged focus of intense activity in the right lobe with absence of activity in the left lobe, consistent with a large AFTN	66%	Suggestive of follicular neoplasm	Hemi-thyroidectomy, final pathology follicular adenoma	TSH normal for 2.4 years after treatment, no thyroid-replacement medication needed
4	Left superior pole is markedly enlarged, right lobe appears normal, consistent with an AFTN	50.1%	Benign	Propylthiouracil	Continues on propylthiouracil, with persistent thyrotoxicosis at time of last outpatient visit
5	Not done	N/A	Benign	N/A	N/A
6	Large hot nodule on the right with a necrotic center, additional faint hot nodule in the left lobe, with suppression of remainder of left lobe	77%	Benign	RAI 21 mCi ^{131}I	TSH normal for 2 years after treatment, no thyroid-replacement medication needed
7	Large hyperfunctioning nodule in the isthmus, with remainder of thyroid tissue suppressed	31.4%	Benign	Hemi-thyroidectomy, developed further nodules and had total thyroidectomy, final pathology hyperplastic nodule with focal lymphocytic thyroiditis	Started on levothyroxine prior to total thyroidectomy
8	Not done	N/A	Benign	Hemi-thyroidectomy, final pathology adenomatous nodule	TSH normal for 1.8 years after treatment, no thyroid-replacement medication needed
9	Hot nodule in the left lobe with partial suppression of the remainder of the gland	22.8%	Not done	RAI 20.7 mCi ^{131}I	1.1 years after treatment developed elevated TSH and symptomatic hypothyroidism, started on levothyroxine
10	Dominant hot right upper pole nodule present, with a small hot nodule in the left upper pole and bilateral lower pole hot nodules, gland is diffusely heterogeneous	14.7%	Benign	RAI 25 mCi ^{131}I	Developed hypothyroidism with an elevated TSH 26 μIU/mL, 3.4 years after treatment
11	Bilateral hot nodules with suppression of activity in the remainder of the gland	27%	Benign	TFTs fluctuation, observation for now, no treatment at this time	Most recent TSH is suppressed 0.16 μIU/mL

(Continued next page)

Table 3 *Continued*

12	Focal area of increased activity in the left lobe consistent with a hot nodule, no evidence of suppression of the remainder of the gland	24.3%	Not done	N/A	N/A
13	Intense focus of uptake in the right lobe with partial suppression of remainder of the gland, consistent with an AFTN	17%	Not done	N/A	N/A
14	Hot nodule in the right lobe with near complete suppression of the remainder of the gland	28%	Benign	Hemi-thyroidectomy, final pathology adenomatoid nodule	N/A
15	Diffuse increased uptake with a more focal area of increased uptake in the right lobe, consistent with Graves disease and a focal hot nodule	52.2%	Benign	RAI 11.8 mCi ^{131}I	Continued to have subclinical hyperthyroidism for 1 year after RAI, started on methimazole
16	Focus of increased activity in the right lobe with suppression of the remainder of the thyroid, representing a hot nodule	31.3%	Not done	RAI 19.7 mCi ^{131}I	TSH normal for 0.2 years after treatment, no thyroid-replacement medication needed
17	Hot nodule in the right lobe with partial suppression of the remainder of the thyroid	39%	Benign	Hemi-thyroidectomy, final pathology adenomatous changes	N/A

Abbreviations: AFTN = autonomously functioning thyroid nodule; FNA = fine-needle aspiration; N/A = not available; RAI = radioactive iodine; TFT = thyroid function test; TSH = thyroid-stimulating hormone; US = ultrasound.

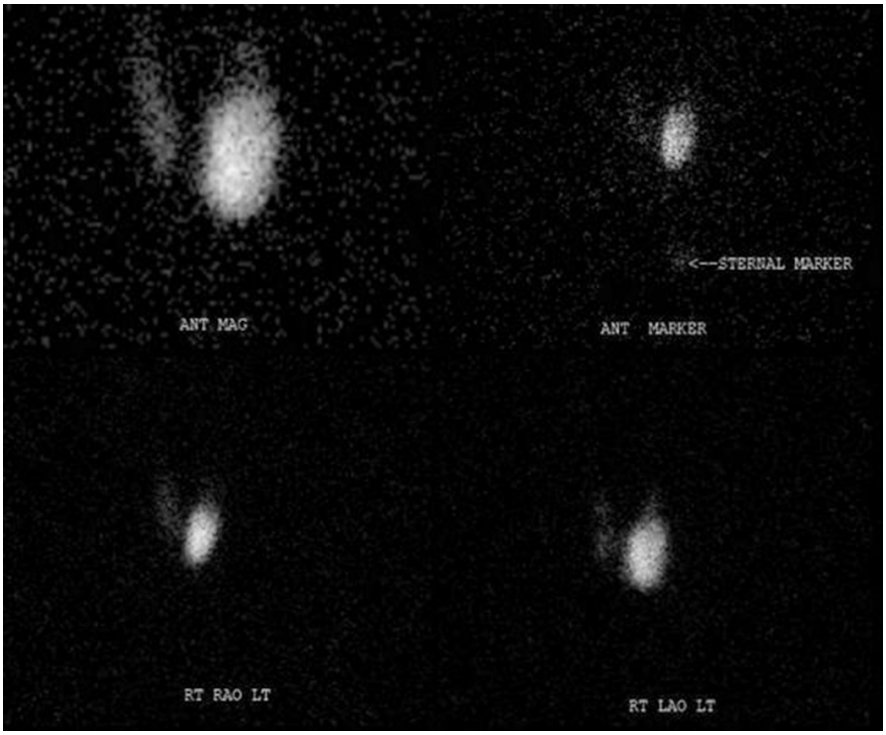

Fig. 2. Thyroid uptake scan of patient 9 showing a 3.8-cm left-sided autonomously functioning thyroid nodule.

an AFTN, although only 6 patients had surgical removal, and final pathology is unknown for the other 11 patients. Treatment of this cohort was by surgery or RAI in approximately equal numbers, with varying rates of requiring subsequent treatment after initial surgery or RAI.

AFTN are benign monoclonal tumors that produce T_3 and T_4 autonomously and that concentrate radioiodine on thyroid uptake scan (5). AFTN is most common in patients 30 to 60 years of age and is rare in pediatrics. It is more common in women than men (6:1 versus 15:1, respectively), as with many thyroid diseases (5). In pediatrics, prior case series also show a female predominance (1-3,12), which was consistent with the findings in our study. It has previously been shown that there is an increased frequency of T_3 toxicosis compared to T_4 toxicosis in AFTN in pediatric patients (3,12,13), which was also consistent with the laboratory findings in our study. In our cohort, 62% of patients had elevated total or free T_3 levels, and only 33% had elevated total or free T_4 levels. The natural history of AFTN is progressive, with one study showing that it can take up to 6 years for an AFTN to progress to hyperthyroidism after diagnosis (13). This progressive increase in function may explain the varying results of 24-hour uptake on thyroid uptake scan seen in our cohort. Although each patient that had a thyroid uptake scan had an area of increased focus consistent with AFTN, only 36% of these patients had an elevated 24-hour uptake. The patients with normal 24-hour uptake may have presented in an early stage of the AFTN before the nodule developed increased uptake above the normal level.

Limitations of this study include retrospective data collection, which limited the data available on the symptoms at presentation and the reasoning for choosing different treatment modalities. Clinical presentation, laboratory results, treatment, and follow-up data were missing for 3 patients in our cohort with AFTN, which limited the analysis of these patients. We elected to include them in our study because there was enough information available to provide a diagnosis of AFTN. The laboratory testing at diagnosis was inconsistent between different providers, with some measuring total T_3 and T_4 levels and some measuring free T_3 and T_4 levels. The evaluation of thyroid antibodies was also inconsistent.

There were 3 patients who did not have a thyroid uptake scan done for evaluation of their thyroid nodule (patients 2, 5, and 8). These patients had a documented thyroid nodule on ultrasound, with suppressed TSH levels. Two of the patients also had negative thyroid antibodies, making AFTN the most likely diagnosis. Patient 2 was subsequently found to have PTC, and without the thyroid uptake scan, it is difficult to make a definitive diagnosis of AFTN in this patient especially. This patient had already seen a pediatric surgeon and had surgery scheduled prior to her appointment with pediatric endocrinology, and a thyroid uptake scan was not done because it would not have affected her clinical management. Although thyroid uptake scans were not done for these patients, we elected to include them in our study because AFTN was the most likely diagnosis based on the data available. If these patients were removed from our analysis, it would not greatly change our results for the demographic and laboratory data of our cohort. This would, however, decrease our number of patients with PTC in AFTN to zero patients, which would be consistent with our conclusion that there is a low rate of PTC in AFTN.

Another limitation is the lack of testing for somatic activating mutations in our population, as this is not routinely done at our institution. Somatic activating mutations of the TSH receptor have been found in up to 48% of AFTN in adults (14). TSH receptor activation stimulates the growth and differentiation of thyrocytes and the secretion of thyroid hormones. These mutations have also been described in pediatrics, with studies showing TSH receptor mutations ranging from 22 to 59% in patients with AFTN (15,16). Mutations of the Gs alpha subunit have also been described but are less common (5,17).

The American Thyroid Association recently published new guidelines with recommendations for evaluation and treatment of thyroid nodules and differentiated thyroid cancers in pediatrics (11). In pediatric patients with an AFTN, the recommendations state that a thyroid uptake scan should be done for evaluation and that surgical resection is the recommended treatment. Surgery may be deferred if asymptomatic, but FNA is not necessary unless there are features suspicious for carcinoma on ultrasound (11). This differs from the previous management of pediatric patients with AFTN, where both surgery and RAI were acceptable treatment modalities. The reasoning stated for changing the recommendations relates to the risk of subsequent malignancy in the remaining thyroid tissue after treatment with RAI as well as the risk of malignancy in the AFTN itself, which may have a delayed diagnosis if treated with RAI. With this change in recommendations, future studies may be able to more accurately assess the prevalence of malignancy in AFTN, as some patients who were treated with RAI may have had malignancies that were undetected.

The prevalence of malignancy in AFTN is one factor that varied widely in prior studies in pediatrics. A study by Niedziela et al (1) in 2002 reported that 29% of pediatric patients with AFTN had cancer. This is significantly higher than other studies, which showed prevalences of 0% (0 of 7 patients) in a study by Osburne et al (12), 12.5% (1 of 8 patients) in a study by de Luca et al (3), and 16.7% (2 of 12 patients) in a study by Croom et al (2). One patient of our cohort of 17 patients with AFTN was found to have cancer, but only 6 patients had surgical removal of their thyroid nodules to determine the final pathology. The rate of cancer in AFTN in our study may then be interpreted as 16.7% (1 of 6 patients), which is within the range that has been seen in prior studies. It has been shown that elevated TSH

levels correlate with increased risk of thyroid carcinoma in the pediatric population and that a low TSH as seen in AFTN has a lower risk of having thyroid carcinoma compared to patients with an elevated TSH (18). This further supports the evidence that the risk of thyroid carcinoma in AFTN is low. The study by Niedziela et al was of patients in Western Poland, where there had been a high prevalence of iodine deficiency, as well as radiation exposure from the Chernobyl nuclear disaster, which is likely the cause of the significantly higher prevalence of thyroid carcinoma in AFTN in their study (1,19).

FNA is one test that is commonly done to evaluate for malignancy in a thyroid nodule. Thirteen patients (76%) in our cohort had an FNA as a part of their evaluation for AFTN, although this has been recommended only for evaluation of a cold thyroid nodule. Even so, the fear of malignancy in thyroid nodules overall has driven providers to obtain an FNA in AFTN where the risk is lower. In addition, many patients found to have a thyroid nodule are first referred to a pediatric surgeon and may already have an FNA performed prior to being evaluated by a pediatric endocrinologist. Unfortunately, in the 1 patient that did have PTC in our cohort, FNA cytology was benign. Similar findings were reported in the study by Niedzela et al (1). In this study of 31 patients with AFTN, 9 patients were found to have thyroid carcinoma. Six of these patients had false-negative pre-operative cytology results. These data, along with results from the patient in our study, suggest that FNA may not be sensitive in detecting malignancy in AFTN and should not be done if the patient is planning to have surgical removal of the nodule. This is consistent with the new guidelines on the evaluation and treatment of thyroid nodules in pediatrics (11). Alternatively, clinical characteristics and ultrasound findings may provide better evidence to determine the risk of malignancy. Some clinical characteristics, including larger nodule size, palpable lymphadenopathy, and palpable thyroid nodule, are more common in patients with thyroid carcinoma compared to patients with benign nodules (20,21). Features on ultrasound that are more suggestive of malignancy include microcalcifications, increased nodular vascularization, and irregular margins of the nodule (21,22). However, these studies were not specific to patients with AFTN, and some characteristics such as a larger nodule size are commonly seen with AFTN.

In our cohort of patients, approximately equal numbers of patients with AFTN were treated with surgery versus RAI. Of the 4 patients who underwent hemi-thyroidectomy and had follow-up data available, there were no patients who developed hypothyroidism or continued to have hyperthyroidism after hemi-thyroidectomy. Two patients required a total thyroidectomy subsequently (1 for PTC and 1 for development of further nodules). Three of the 5 patients that were treated with RAI required further treatment (2 for hypothyroidism and 1 for continued hyperthyroidism), and the remaining 2 patients subsequently had normal thyroid function and did not require further treatment. Patient 15, who continued to have hyperthyroidism following RAI, also had a diagnosis of Graves disease, which is a confounding factor. Although there are no pediatric studies that look at outcomes following RAI treatment for AFTN, adult studies show varying results of developing hypothyroidism, ranging from 8 to 36% after RAI treatment, and 7 to 15% of patients required subsequent doses of RAI due to continued hyperthyroidism (23-25). The inconsistency of results after RAI treatment further supports the new American Thyroid Association guidelines in recommending surgical removal of AFTN for pediatric patients (11).

CONCLUSION

We concur with the new guidelines for evaluation and management of AFTN in pediatrics, which recommend treatment with surgical resection only and do not recommend FNA prior to surgery (11). Treatment of our cohort prior to the publication of these guidelines was by surgery or RAI in approximately equal numbers, and many patients treated with RAI had subsequent hypothyroidism or hyperthyroidism after treatment. There was a low rate of malignancy in our cohort of patients with AFTN in a population that has sufficient iodine levels. However, it is possible that some cases were missed if not surgically removed, as FNA in our population was not sensitive in screening for cancer in AFTN.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Niedziela M, Breborowicz D, Trejster E, Korman E.** Hot nodules in children and adolescents in western Poland from 1996 to 2000: clinical analysis of 31 patients. *J Pediatr Endocrinol Metab*. 2002;15:823-830.
2. **Croom RD 3rd, Thomas CG Jr, Reddick RL, Tawil MT.** Autonomously functioning thyroid nodules in childhood and adolescence. *Surgery*. 1987;102:1101-1108.
3. **de Luca F, Chaussain JL, Job JC.** Hyperfunctioning thyroid nodules in children and adolescents. *Acta Paediatr Scand*. 1986;75:118-123.
4. **Grob F, Deladoëy J, Legault L, et al.** Autonomous adenomas caused by somatic mutations of the thyroid-stimulating hormone receptor in children. *Horm Res Paediatr.* 2014;81:73-79.
5. **Corvilain B, Dumont J, Vassart G.** Toxic adenoma and toxic multinodular goiter. In: Braverman L, Utiger R, eds. *Werner and Ingbar's The Thyroid: A Funamental and Clinical Text*. 8th ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2000: 564-572.
6. **Corrias A, Mussa A, Baronio F, et al.** Diagnostic features of thyroid nodules in pediatrics. *Arch Pediatr Adolesc Med*. 2010;164:714-719.

7. **Gupta A, Ly S, Castroneves LA, et al.** A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. *J Clin Endocrinol Metab*. 2013;98:3238-3245.
8. **Niedziela M.** Pathogenesis, diagnosis and management of thyroid nodules in children. *Endocr Relat Cancer.* 2006;13: 427-453.
9. **Tfayli HM, Teot LA, Indyk JA, Witchel SF.** Papillary thyroid carcinoma in an autonomous hyperfunctioning thyroid nodule: case report and review of the literature. *Thyroid*. 2010;20:1029-1032.
10. **Hung W, August GP, Randolph JG, Schisgall RM, Chandra R.** Solitary thyroid nodules in children and adolescents. *J Pediatr Surg*. 1982;17:225-229.
11. **Francis G, Waguespack SG, Bauer AJ, et al.** Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2015;25:716-759.
12. **Osburne RC, Goren EN, Bybee DE, Johnsonbaugh RE.** Autonomous thyroid nodules in adolescents: clinical characteristics and results of TRH testing. *J Pediatr.* 1982;100: 383-386.
13. **Hamburger JI.** Evolution of toxicity in solitary nontoxic autonomously functioning thyroid nodules. *J Clin Endocrinol Metab*. 1980;50:1089-1093.
14. **Krohn K, Führer D, Holzapfel HP, Paschke R.** Clonal origin of toxic thyroid nodules with constitutively activating thyrotropin receptor mutations. *J Clin Endocrinol Metab*. 1998;83:130-134.
15. **Eszlinger M, Niedziela M, Typlt E, et al.** Somatic mutations in 33 benign and malignant hot thyroid nodules in children and adolescents. *Mol Cell Endocrinol*. 2014;393: 39-45.
16. **Agretti P, Segni M, De Marco G, et al.** Prevalence of activating thyrotropin receptor and Gs-α gene mutations in paediatric thyroid toxic adenomas: a multicentric Italian study. *Clin Endocrinol (Oxf)*. 2013;79:747-749.
17. **Schwab KO, Pfarr N, van der Werf-Grohmann N, et al.** Autonomous thyroid adenoma: only an adulthood disease? *J Pediatr.* 2009;154:931-933.e2.
18. **Chiu HK, Sanda S, Fechner PY, Pihoker C.** Correlation of TSH with the risk of paediatric thyroid carcinoma. *Clin Endocrinol (Oxf)*. 2012;77:316-322.
19. **Niedziela M, Korman E, Breborowicz D, et al.** A prospective study of thyroid nodular disease in children and adolescents in western Poland from 1996 to 2000 and the incidence of thyroid carcinoma relative to iodine deficiency and the Chernobyl disaster. *Pediatr Blood Cancer.* 2004;42:84-92.
20. **Buryk MA, Simons JP, Picarsic J, et al.** Can malignant thyroid nodules be distinguished from benign thyroid nodules in children and adolescents by clinical characteristics? A review of 89 pediatric patients with thyroid nodules. *Thyroid*. 2015;25:392-400.
21. **Mussa A, De Andrea M, Motta M, Mormile A, Palestini N, Corrias A.** Predictors of malignancy in children with thyroid nodules. *J Pediatr.* 2015;167:886-892.
22. **Corrias A, Mussa A.** Thyroid nodules in pediatrics: which ones can be left alone, which ones must be investigated, when and how. *J Clin Res Pediatr Endocrinol*. 2013;5(suppl 1):57-69.
23. **Goldstein R, Hart IR.** Follow-up of solitary autonomous thyroid nodules treated with 131I. *N Engl J Med*. 1983;309: 1473-1476.
24. **Nygaard B, Hegedüs L, Nielsen KG, Ulriksen P, Hansen JM.** Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. *Clin Endocrinol (Oxf)*. 1999;50:197-202.
25. **Ronga G, Filesi M, D'Apollo R, et al.** Autonomous functioning thyroid nodules and 131I in diagnosis and therapy after 50 years of experience: what is still open to debate? *Clin Nucl Med*. 2013;38:349-353.