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Fine Needle Aspiration Cytology of Pediatric Thyroid Nodules

Pediatrik Tiroid Nodüllerinde İnce İğne Aspirasyon Sitolojisi

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ABSTRACT

Objective: The objectives were to evaluate fine needle aspiration cytology results of 39 pediatric patients, and the pathologies that cause childhood thyroid nodules, and to review the literature on the subject.

Material and Method: Thyroid fine needle aspiration cytology results of 39 pediatric patients were retrospectively reviewed. Associated diseases, thyroid functions, anti-thyroid antibody levels, ultrasonographic findings and number of nodules were also evaluated.

Results: The vast majority of patients with thyroid nodules were cytopathologically diagnosed as benign (97.3%). Of these patients, 64.8% (24 patients) were diagnosed as nodular goiter and 35.2% (13 patients) as lymphocytic thyroiditis. Thyroid malignancy was found in two patients; one was diagnosed as follicular neoplasm/minimal invasive follicular carcinoma on surgical evaluation while the other was a secondary tumor (Burkitt's lymphoma). The majority of our subjects were females (66.6%): the female/male ratio was 2:1 for nodular goiter and 3.3:1 for thyroiditis. Surgical resection was performed in 5 patients (4 cases of nodular goiter, 1 suspicious for malignancy) and cytological diagnoses were confirmed by histology.

Conclusion: Our study confirmed the utility of fine needle aspiration cytology in childhood thyroid disorders along with a possible higher incidence of nodular thyroiditis in childhood. Nodular autoimmune thyroiditis, focal thyroiditis and thyroid cancer in children are discussed and attention is drawn to some special subtypes of thyroid cancer and some benign lesions that can cause difficulty in interpreting fine needle aspiration cytology and frozen sections at this age.

Key Words: Pediatric thyroid nodules, Thyroid nodules, Cytology, Fine needle aspiration cytology

ÖZ

Amaç: 39 çocuk hastanın ince iğne aspirasyon sitolojisi sonuçlarının; nodül oluşumuna neden olan patolojilerin incelenmesi ve konu ile ilgili literatürün gözden geçirilmesi amaçlandı.

Gereç ve Yöntem: 39 çocuk hastanın tiroid ince iğne aspirasyon sitolojisi sonuçları gözden geçirildi. Eşlik eden hastalıklar, tiroid fonksiyonları, anti-tiroid antikor seviyeleri, ultrason bulguları ve nodül sayısı incelendi.

Bulgular: Tiroid nodüllerinin çoğu sitopatolojik olarak benign (%97,3) tanısı aldı. Bunların %64,8'i (24 hasta) sitopatolojik olarak nodüler guatr, %35,2'si (13 hasta) ise lenfositik tiroidit tanısı aldı. İki hastada tiroid malignitesi saptandı; birisi histopatolojik olarak folliküler neoplazi/minimal invaziv folliküler karsinom, diğeri ise sekonder bir malignite olup, Burkitt lenfoma tanısı aldı. Bu seride kız hastalar çoğunluğu oluşturmaktaydı (%66,6): nodüler guatr için kız/erkek oranı 2:1, lenfositik tiroidit için ise 3.3:1 idi. Sitopatolojik tanısı nodüler guatr olan 4 olguda ve kuşkulu sitoloji olan 1 olguda histopatolojik doğrulama yapıldı.

Sonuç: Bu çalışmada, çocukluk çağı tiroid patolojilerinde ince iğne aspirasyon sitolojisinin yararlılığı gösterildi. Ayrıca çocukluk çağında nodüler tiroidit insidansının muhtemel yüksekliğine dikkat çekildi. Pediatrik nodüler otoimmün tiroidit, fokal tiroidit ve tiroid kanseri tartışıldı ve bu çağdaki tiroid ince iğne aspirasyon sitolojisi ve dondurulmuş kesit incelemelerinin yorumunda güçlüğe neden olabilecek bazı benign lezyonlara dikkat çekildi.

Anahtar Sözcükler: Pediatrik tiroid nodülleri, Tiroid nodülleri, Sitoloji, İnce iğne aspirasyon sitolojisi

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INTRODUCTION

The incidence of thyroid nodules in children by clinical examination is estimated at 1-1.5%. The incidence of a thyroid nodules in the general population is 19-35%. Malignancy develops in less than 5% of these (1) while this rate can go up to 25% in childhood thyroid nodules (1-5). There are also reports of a low incidence (2%) of malignancy development in nodules in this age (6).

Childhood thyroid nodules may develop due to nodular hyperplasia, thyroiditis (Hashimoto and Graves), malignancy, congenital hypothyroidism (dyshormonogenetic goiter), thyroid hemiagenesis and thyroglossal ductus cyst. Fine needle aspiration cytology (FNAC) has been reported to provide sensitivity, specificity and possible use of cytological criteria in children that are similar to adults (1,7). There are only a few pediatric series of thyroid nodules and their reported thyroiditis and malignancy rates vary with reported thyroiditis rates of 2 to 48% and malignancy rates of 2 to 50% (1,3,4,6-15). There are also few studies on the thyroiditis-thyroid cancer association in childhood. A series of 365 autoimmune thyroiditis (AIT) cases in children reported a nodule in 115 (31%) of which 11 (3%) were malignant (4). There are again very few reports on some thyroid carcinoma types (16,17,18) and entities (19) that seem to be specific to childhood.

The aim of this study was to investigate the results of FNAC in childhood pediatric thyroid nodules, evaluate the association between thyroid pathologies and thyroid cancer, observe some demographic characteristics of childhood thyroid pathologies and to increase the sensitivity of a multidisciplinary approach to these cases. We also correlated the hormonal status, thyroid antibody level and ultrasonography (USG) results of these cases with their FNAC results. Another aim of this study was to review the literature data on the clinicopathological analysis of pediatric thyroid nodules.

MATERIAL and METHOD

The study was retrospective in nature. A total of 50 thyroid fine needle aspiration (FNA) material from 47 cases were found between 2005 and 2009 in the Pathology Clinic archives. The classical four-way classification system was used for cytopathological diagnoses. The cases were divided into benign, malignant, suspicious and nondiagnostic categories. 8 nondiagnostic cases were excluded from the study. 42 thyroid FNA material of 39 cases were evaluated once again by 2 pathologists and the cytopathological findings and diagnosis distribution were evaluated. A table was also made of the gender, age, concurrent disease, presentation symptom, hormonal status, antibody levels and USG results of the cases. FNA was performed by a radiologist under USG, using a 21 gauge needle. There were no complications during the procedure. Part of the smear was air-dried and stained with May-Grünwald-Giemsa while the other part was fixed with 95% alcohol and stained with PAP in all cases. Sections were obtained from the surgical specimens after paraffinization and H&E applied.

RESULTS

The age range was 4-18 years with a mean age of 11±1. Our series had 26 females (66.6%) and 13 males (33.3%) (F:M=2:1). Nodular goiter (NG) was diagnosed in 24 patients with 16 females and 8 males (F:M=2:1). There were 13 chronic lymphocytic thyroiditis (CLT) patients with 10 females and 3 males (F:M=3.3:1).

All cases except two presented with a neck swelling. One of the two cases was a nodular goiter case diagnosed with a high TSH level while being followed-up for Hodgkin's lymphoma. The other case had thyroiditis and had presented with shortness of stature and developmental retardation.

Laboratory results:

Thyroid function test results of 13 NG cases were available and 10 were euthyroid, 3 hypothyroid. Of the thyroiditis cases, 4 were euthyroid and 2 hypothyroid.

Antithyroid antibody levels of 11 NG cases were known and only 1 had high antithyroid peroxidase (anti TPO) levels. This was a multinodular goiter case who also suffered from the McCune-Albright syndrome and the results of both FNA procedures performed with a 2-year interval were consistent with NG. Antithyroid antibody levels were known in 6 thyroiditis cases and 4 had high antibody titers while 2 were negative.

USG findings:

There was a single thyroid nodule or multiple nodules in all cases except the three thyroiditis cases. There was a single nodule in 8 and multiple nodules in 16 of the 24 NG cases on USG. The nodules were hypoechogenic and heterogenous in 11 cases, isoechogenic and heterogenous in 3 cases and hypoechogenic and homogenous in 5 cases. Parenchyma was heterogenous in only 3 cases.

No nodule was found on USG in the thyroid parenchyma of 3 of the 13 CLT cases; the gland was generally heterogenous and hypoechogenic. There was a single hypoechogenic and/or heterogenous nodule in 6 cases and multiple

heterogenous and hypoechogenic nodules in 4 cases. The gland parenchyma was homogenous in 4 of these cases and heterogenous in 1 case.

Another pathology (1 McCune-Albright Syndrome, 1 Hodgkin's lymphoma) accompanied only 2 NG cases out of the 39 cases in total.

Cytopathological findings:

Of the 42 FNA cases, 40 were evaluated as benign (27 NG, 13 CLT), 1 suspicious for malignancy and 1 malignant (Burkitt's lymphoma).

Cytopathological analysis of NG cases showed a colloid background with groups of thyrocytes that were mostly arranged in sheets but consisted micro- or macrofollicular structures in some parts and, in some cases, foamy histiocytes and stromal fragments.

Cytologic preparations of thyroiditis cases were generally poor in thyrocytes and contained little colloid. The polymorphic lymphoid infiltrate was striking in these cases (Figure 1).

The case where malignancy was suspected was 7 years old and had presented with a neck mass and hypothyroidism. USG showed a homogenous, isoechogenic, solid nodule in the right thyroid lodge that was cold on scintigraphy with a size of 3.5x3.2 cm and a partial peripheral halo. The rest of the parenchyma was homogenous. Aspiration cytology showed thyrocytes that had a metaplastic appearance with eccentric nuclei in places, containing pseudoinclusion-like structures with a high nucleus/cytoplasm ratio that were distributed as microfollicular and papillary structures in a colloid-poor background and foamy macrophages with nuclei showing atypical endocrine appearance (Figure 2A, B). The case was thought to be suspicious for malignancy with these cytological findings but no differentiation was made between a follicular neoplasm and papillary neoplasm. Histopathological examination revealed a solid nodule with scattered calcification areas consisting of thyroid follicules of various sizes that contained papillary structures in part. The nuclei were large and vesicular but there were no diagnostic findings of papillary carcinoma (PC). There was an extracapsular area of suspicious vascular invasion that stained positive immunohistochemically with mesothelin. The capsule invasion could not be clearly demonstrated and the case was therefore accepted as follicular neoplasm (minimal invasive carcinoma?). The case has been followed-up for 3 years without recurrence.

There were synchronous thyroid and intraabdominal masses in the case diagnosed as malignant. FNA evaluation

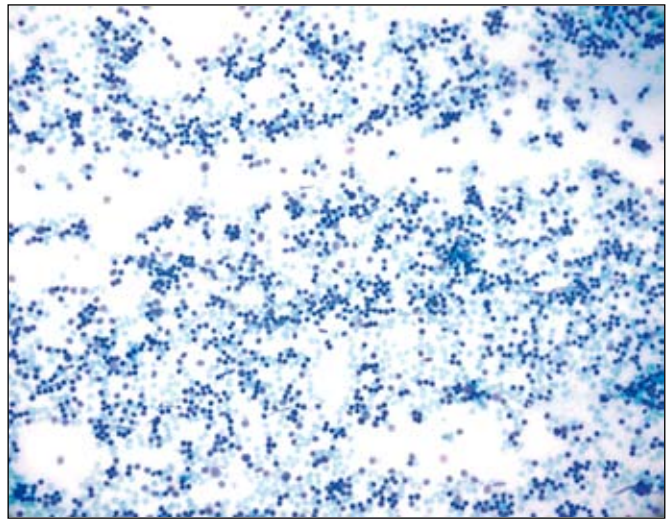

Figure 1: Lymphoid cells at various stages of maturation (MGG, x100).

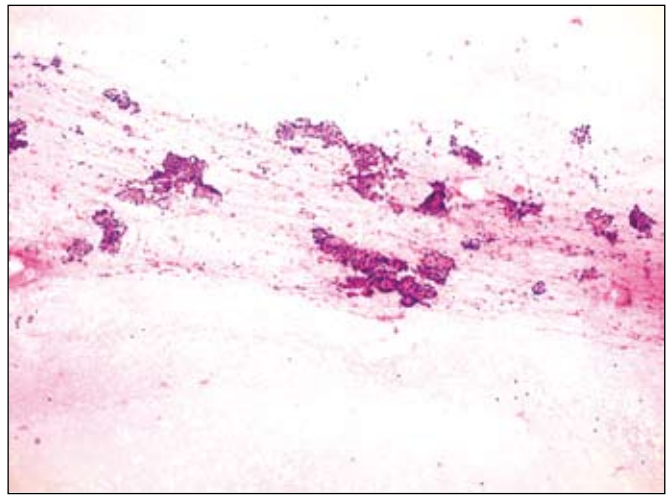

Figure 2A: Hypercellularity, papillary and microfollicular structures (H&E, x100).

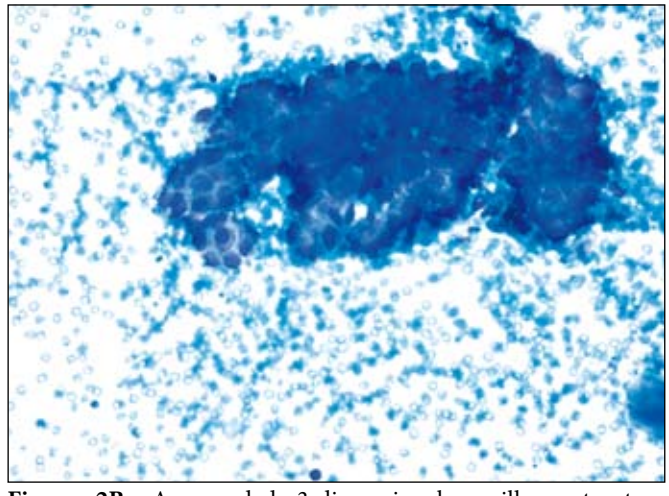

Figure 2B: A crowded 3-dimensional papillary structure consisting of cells with a high N/C ratio (MGG, x200).

of the thyroid showed an atypical cell population consisting of cells of moderate size with a monotonous appearance and round nuclear borders with microvacuoles in their narrow basophilic cytoplasms (Figure 3). The case was reported as consistent with lymphoma (primarily Burkitt). The histopathological and immunohistochemical evaluation results of the tru-cut biopsy material from the intraabdominal mass also supported the diagnosis of Burkitt's lymphoma.

Four of the 5 cases that underwent surgical resection had NG and one had findings suspicious for malignancy on cytopathology. The histopathological results were found to be consistent with the FNA results in all cases.

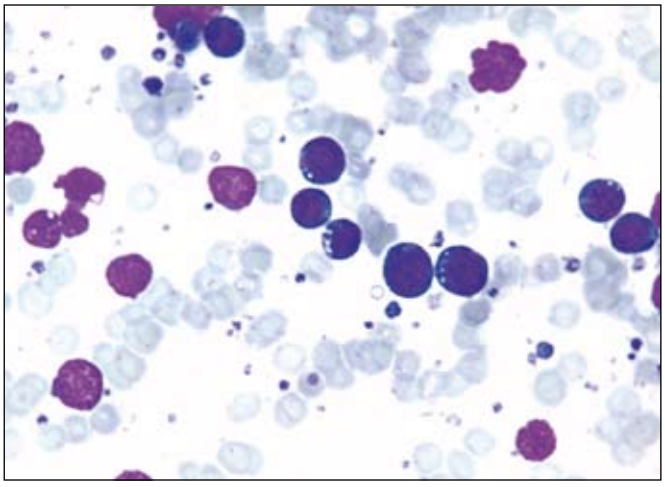

Figure 3: Tumor cells of moderate size with monotonous appearance and round shape, containing paranuclear microvacuoles (MGG, x1000 imm. oil).

DISCUSSION

FNA is a relatively simple procedure with a low complication rate. This procedure has become a routine part of thyroid nodule investigation in adults but is still not in common use in childhood thyroid nodules. Excellent results have been reported for thyroid FNA procedures. Some reports have emphasized a marked superiority to USG and scintigraphy in differentiating malignant and benign lesions (1). High sensitivity and specificity rates are also reported when compared with cases where only antibody titers are evaluated for AIT diagnosis (12,14,20,21). The sensitivity and specificity further increases when used together with serology, USG and FNA. The success of FNA procedure is directly influenced by the performing person's experience (adequate and correct sample that represents the lesion) and the competence of the pathologist interpreting the findings. Both these factors determine the false-positive and true-negative rates.

Analysis of thyroid pathology series in childhood shows that females make up the majority of cases (75-90%) (1,4,9) and that the mean age generally corresponds to childhood and adolescence (12.5-17 years) (1,7,9,16,21,22). Some reports have a higher incidence of male patients when malignancy is present (4,22). Females made up 66.6% of the cases in our series and the mean age was 11+/-1. NG (61.5%) and CLT (33.3%) made up the majority of the thyroid nodules in our study. A thyroid malignancy was found in 2 of the 39 cases included in the study (5.2%). Surgical procedure was used in a total of 5 cases (1 malignant in 4NG). The histopathology results were consistent with FNA results in all these cases.

Evaluation of the rates of benign cases and CLT in adult series of FNA in the literature has shown a rate of 62-64% for benigncases (23,24) while thyroiditis rate is 1-11% (23,25). The rate of thyroiditis in childhood thyroid nodules in our series (33%) was significantly higher than adult series. This result needs to be supported with larger series in this age group.

Thyroid carcinomas are rare solid tumors of childhood. Pediatric thyroid nodules are reported to be less frequent than adult nodules but to contain malignancy more often while pediatric well-differentiated thyroid carcinomas show earlier spread to the surrounding tissues and lymph nodes compared to adult forms and distant metastases and recurrences are more common (1-5). Despite all these unfavorable elements, pediatric thyroid carcinomas generally have a much better prognosis than their adult counterparts with an almost 100% disease-free survival (4,22,26). The association of the prognosis with age is frequently emphasized (27,28). PC constitutes the majority of childhood thyroid carcinomas (60%, 68%, 91%, 93%) (16,18,22,29). Other common types are, in order of frequency, follicular carcinoma, medullary carcinoma and Hürthle cell carcinoma. Thyroid PC has been reported to possibly have a special form in children younger than 10 years that consists of a combination of follicular and solid areas with nuclear pseudoinclusions and nuclear border irregularities but without classical PC findings such as nuclear notching that usually shows widespread psammoma bodies and infiltration within the whole gland (16).

Although the incidence of malignancy in our series falls within the range reported in the literature, it may be better to increase the number of cases in the series. We believe that the rates varying between 2 and 50% in the literature are partly due to the way the series are formed and depend

on whether they are from an oncology reference hospital or not.

AIT is the most common cause of goiter in the pediatric age group after iodine deficiency. The most common causes are Hashimoto's thyroiditis (HT) and Graves' disease. HT is more common in childhood and the atrophic form is rare. The diagnosis is made with antibody titers and/or FNA (12). There are varied reports of the prevalence of a nodule in pediatric AIT cases. Some publications report all AIT cases as diffuse goiter (12) while others report various incidences of nodule development (3.3%, 31%, 27.8%, 28%) (4,21,30,31). Most (77%) of the CLT cases diagnosed via FNA in our clinic had a single nodule or multiple nodules. None of the cases were malignant. The lack of series in the pediatric age group in the literature has led to very few nodular AIT cases studied in childhood (3,4). A report with 365 pediatric AIT cases has found a nodule incidence of 31% with a cancer incidence of 9.6% (all PC) in these nodules (4). Although the cytomorphological findings overlap between children and adults for CLT, possibly less prominent fibrosis and germinal centers and Hürthle cell changes in children must be taken into account (20). The smear results of thyroiditis cases in our study supported these findings. The smears generally contained few thyrocytes with a dense lymphoid infiltrate and little colloid.

In conclusion, FNAC is an effective method for the differential diagnosis of thyroid pathologies and thyroid nodules but we would like to emphasize some characteristics of this age group:

1) There are reports of focal thyroiditis accompanying pediatric PC (5,32,33). Pediatric nodular lymphocytic thyroditis cases that are FNAB (+) but have repeated negative autoantibody levels need close monitoring and surgery may be required to exclude a neoplasm (25). Cases of nodular thyroiditis with inadequate content require repeat biopsy.

2) Childhood thyroid carcinomas can differ from adult forms; the PC subtypes of this age are childhood papillary carcinoma (16) and diffuse sclerosing PC that may blend in with a clinical picture of serology (+) thyroiditis (17,18).

3) The FNAB and frozen procedures from the nodules that develop on a base of dyshormonogenetic goiter and the pediatric solitary papillary hyperplastic thyroid nodules (hot nodule with autonomous function) can lead to diagnostic difficulties and misinterpretations. These cases can be differentiated from PC with the clinical history, and FNAC findings of cytoplasmic marginal vacuoles, non-branching short papillae, the lack of nuclear pseudoinclusions and the presence of a large colloid content (18,19).

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