INTRODUCTION

Thyroid nodules are uncommon in children and adolescents compared with adults, but the risk of malignancy is much higher. In adults, fine needle aspiration biopsy (FNAB) has been used extensively to select patients for surgical exploration with a high degree of reliability. The purpose of this study was to assess the utility of FNAB for the management of thyroid nodules in children and adolescents. We reviewed our experience with 60 FNABs of thyroid nodules in 51 children and adolescents. Of the 60 aspirates, 45 aspirates (74%) were diagnosed as "benign", 5 aspirates (8%) as "suspicious for malignancy", and 6 aspirates (10%) as "malignant", and 4 aspirates (7%) as "unsatisfactory". Thyroidectomy was performed in 17 patients, and 5 with a cytological diagnosis of "benign" revealed nodular hyperplasia in three and follicular adenoma in two; 5 with a cytological diagnosis of "suspicious" revealed nodular hyperplasia in one, follicular adenoma in two, and papillary carcinoma in two; and 6 with a cytological diagnosis of "malignant" revealed papillary carcinoma. One patient with a cytological diagnosis of "unsatisfactory" revealed papillary carcinoma. The diagnostic accuracy was 81% with 100% sensitivity and 63% specificity. The positive and negative predictive values of FNAB were 73% and 100%, respectively. We conclude that FNAB is a good screening test for thyroid nodules in children and adolescents because of its high sensitivity.

MATERIALS AND METHODS

The reports of thyroid FNAB performed in 51 children and adolescents at the Inje University Ilsan Paik Hospital were reviewed. Eighty one percent of the procedures were performed by three cytopathologist, using 23 gauge needles connected to 10 mL syringes. In these cases, cytological material was smeared immediately onto slides. Some of the slides were air dried and stained with Diff-Quik stain for an immediate evaluation of specimen adequacy. Other slides were immediately alcohol-fixed and stained with Papanicolaou stain. The remaining procedures were performed by radiologists. All of these slides were alcohol-fixed and sent to our laboratory for staining and evaluation. FNAB results were classified into three categories: 1) malignant, when the aspirates had unequivocal cytological findings of malignancy; 2) suspicious for malignancy, including follicular neoplasms and aspirates that showed some features of papillary carcinoma, e.g., a few cells with intranuclear inclusions or nuclear grooves but without sufficient criteria for a definitive diagnosis of malignancy; and 3) benign, including nodular hyperplasia, colloid cyst, and thyroiditis. Aspirates with less than at least six clusters of well preserved follicular cells on two slides were considered unsatisfactory (1).
patients’ ages ranged from 2 to 21 yr with a mean age of 17 yr. Sixteen (27%) of the patients were 2 to 15 yr old. Thirty-eight (75%) were female and thirteen (25%) were male. Cytological findings are summarized in Table 1 and 2. Forty-five (74%) of the aspirates were diagnosed as “unsatisfactory”. The cytological diagnosis in three cases was Hashimoto’s thyroiditis. Five (8%) of the aspirates were diagnosed as “suspicous for malignancy”. Four of these aspirates were further diagnosed as follicular neoplasm and one was suspicious for papillary carcinoma. Six (10%) of the aspirates were diagnosed as “malignant” and further diagnosed as papillary carcinoma. Four (7%) of the aspirates were “unsatisfactory” (Table 1).

The surgical outcomes of 17 patients who underwent thyroidectomy are summarized in Table 3. Of 5 patients with a cytological diagnosis of “benign”, three had nodular hyperplasia and two follicular adenoma. Of 4 patients with a cytological diagnosis of “follicular neoplasm”, one had nodular hyperplasia, two had follicular adenoma, and one papillary carcinoma. One patient with a cytological diagnosis of “suspicous for papillary carcinoma” had papillary carcinoma. All 6 patients with a cytological diagnosis of “malignant” revealed papillary carcinoma. One of 4 patients with a cytological diagnosis of “unsatisfactory” underwent surgery and was found to have papillary carcinoma. Other cases were followed up clinically without surgical intervention (Table 2).

The cases “suspicous” or “malignant” by cytological diagnosis that were found to have a malignant lesion at surgery were considered “true positive.” “True negative” cases comprised cases considered “benign” with a benign lesion, including follicular adenoma, on resection. Using these criteria, the diagnostic accuracy of FNAB was 81% with a sensitivity of 100% and a specificity of 63%. Positive and negative predictive values were 73% and 100%, respectively, and false negative and positive values were 0% and 37%, respectively.

Three false positive cases were diagnosed as “follicular neoplasm” on FNAB but revealed nodular hyperplasia or follicular adenoma on surgical resection. The cytological findings of these cases were the presence of syncytial fragments, a microfollicular pattern, and nuclear grooves (Fig. 1). Two of 5 true negative cases revealed follicular adenoma on surgical resection. These cases showed some clusters of follicular epithelial cells and a few scattered macrophages in the bloody background (Fig. 2).

Table 1. Cytological diagnoses by fine needle aspiration biopsy

| Diagnostic category | Age group | No. of cases |
|---------------------|-----------|--------------|
|                     | 2-15 yr old (%) | 16-21 yr old (%) |                 |
| Malignant           | 2 (13%) | 4 (9%) | 6 (10%) |
| Suspicious          | 1 (6%) | 9 (9%) | 5 (8%) |
| Benign              | 13 (81%) | 32 (73%) | 45 (74%) |
| Unsatisfactory      | 0 (0%) | 4 (9%) | 4 (7%) |
| Total               | 16 | 44 | 60 |

Table 2. Relation between cytological diagnosis and histological diagnoses of resected thyroid nodules in children and adolescents

| Cytological diagnosis | Histological diagnoses | Total |
|-----------------------|------------------------|-------|
|                       | Nodular hyperplasia    | Follicular adenoma | Papillary carcinoma |
| Malignant             | 0                      | 0                 | 6                 |
| Suspicious for papillary carcinoma | 0 | 0 | 1 |
| Follicular neoplasm   | 1                      | 2                 | 1                 |
| Benign                | 3                      | 2                 | 0                 |
| Unsatisfactory        | 0                      | 0                 | 1                 |
| Total                 | 4                      | 4                 | 9                 | 17 |
up group. If this group were considered true negative in the present study, specificity increases to 94%. Another statistical problem concerns the precise definition of false positive and false negative. In our studies, for statistical analysis, cases with a suspicious or malignant cytological diagnosis that had a malignant lesion at surgery were considered true positives (9, 10). Using these criteria, the sensitivity and specificity of thyroid FNAB were 100% and 63%, respectively. Follicular adenomas and carcinomas are both neoplastic lesions and their differentiation usually requires surgical excision and examination of entire nodules. Therefore, in some studies, the cases with a cytological diagnosis of suspicious or positive for malignancy and a histological diagnosis of follicular neoplasms encompassing both follicular adenoma and follicular carcinoma are considered true positive results. And, using these criteria, the sensitivity and specificity of our study would have been 83% and 75%.

Even if the statistical problems were considered, the reported specificities including ours had a wide range of figure and were sometimes disappointing. These are due to the existence of follicular neoplasms. Follicular neoplasms have generally been considered a diagnostic “gray zone” in thyroid FNAB. Included in this group are hyperplastic nodules of goiters, follicular adenomas, and follicular carcinomas. Because of overlapping cytologic features, a diagnosis of follicular carcinoma is usually made after examining permanent sections follow-

Fig. 1. (A) Fine needle aspiration biopsy finding of follicular neoplasm confirmed as a follicular adenoma. The aspirate shows syncytial fragments (Papanicolaou, × 200). (B) The loosely cohesive follicular cells show nuclear grooves (Papanicolaou, × 400). (C) On histologic finding, the follicular cells show nuclear grooves (H&E, × 400).
Surgical treatment. The overall rate of malignancy in nodules with cytological diagnosis of follicular neoplasm has been reported as approximately 20-30% (16). Kim et al. reported that 50% of such patients were diagnosed as malignancy, and an age below 20 yr (77%) had a significant increased risk for malignancy (16). In the present study, one of four cases with a cytological diagnosis of follicular neoplasm revealed papillary carcinoma. This figure is lower than that of Kim et al. but is similar to the overall rate of 20-30%.

In our false positive cases, the presence of syncytial fragments, a microfollicular pattern, and nuclear grooves misled a cytological diagnosis of follicular neoplasm. The nuclear grooves are a non-specific feature which can be seen in cases of Hashimoto's thyroiditis, nodular hyperplasia with oncocyes, follicular adenoma, or Hurthle cell adenoma (5). Of five present cases with a cytological diagnosis of benign, two cases were histologically diagnosed as follicular adenoma. These cases showed some clusters of atrophic follicular epithelial cells and a few scattered macrophages in the bloody background. Yang et al. suggested the most important clue in differentiating follicular neoplasm from nodular hyperplasia was "abundant blood containing microfollicles" (17). However, macrofollicular adenomas have far lower microvessel density than microfollicular nodules because the space occupied by the large colloid lakes are devoid of blood vessels. Therefore, macrofollicular adenomas will be diagnosed as nodular hyperplasia by FNAB. Likewise, a discrete but unencapsulated microfollicular nodule will be diagnosed as "follicular neoplasm" by FNAB, resulting in the excision of nonneoplastic nodules.

Some reports have suggested that the cases diagnosed as follicular neoplasm on thyroid can be stratified into lesions with a high risk of malignancy and with a low risk of malignancy that can be managed by clinical observation alone on the basis of clinical characteristics such as large size of the index nodule (lesions measuring 3 cm or larger) and male sex (18). However, we experienced that one papillary carcinoma of a cytological diagnosis of follicular neoplasm was female and her thyroid nodule measured 1.8 cm in diameter. In another three cases revealed follicular adenoma or nodular hyperplasia, the ratio of male:female was 1:2 and their nodule measured 3.3 cm to 3.4 cm in diameter. Although clinical characteristics can help in selecting patients for surgery, the final diagnosis by histological examination is needed. Several reports have suggested that the use of immunohistochemical markers such as cytokeratin-19, galectin-3, and HBME-1 are useful in FNAB specimens of the thyroid to differentiate between benign and malignant lesions (19-21). But some benign thyroid nodules can also stain with these markers.

We concluded that FNAB is a good screening test for thyroid nodules in children and adolescents because of its high sensitivity. However, the additional use of various clinical variables and immunohistochemical markers can be helpful to differentiate in follicular neoplasms in FNAB.

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Fig. 2. Fine needle aspiration biopsy finding of nodular hyperplasia confirmed as a follicular adenoma. The aspirate shows loosely cohesive follicular cells in the bloody background (Papanicolaou, ×200).
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