Accuracy of Fine Needle Aspiration Biopsy of Thyroid Nodules in Detecting Malignancy in Childhood: Comparison with Conventional Clinical, Laboratory, and Imaging Approaches


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In childhood the traditional diagnostic approach to thyroid nodules consists of clinical, laboratory, and imaging evaluations. A safe and accurate procedure is needed to promptly identify patients who require surgery.

In regard to the usefulness of fine needle aspiration biopsy, the data in the literature concerning children and adolescents are scanty. The aim of this study was to evaluate and compare the diagnostic accuracies of clinical, laboratory, and imaging data collected retrospectively in a group of pediatric patients with thyroid nodules submitted to fine needle aspiration biopsy.

Forty-two patients who underwent surgery for thyroid nodules, recruited in 9 Italian pediatric endocrine units, were retrospectively studied. According to histological diagnosis, they were divided into 2 groups, 22 patients with benign lesions and 20 patients with malignant lesions. From clinical records we obtained data about 1) symptoms of neck compression; 2) cervical adenopathy; 3) thyroid function, calcitonin level, and antithyroid antibody titers; 4) ultrasonography; 5) 99mTc scintiscanning; and 6) cytology obtained with fine needle aspiration biopsy. Patients and nodule characteristics were analyzed statistically for associations with the presence of thyroid cancer.

Among clinical findings, only adenopathy was significantly higher in the group with cancer (8 of 22 benign lesions vs. 16 of 20 malignant lesions; P = 0.006). Thyroid function and antithyroid antibody titers were similar in the 2 groups, whereas the serum calcitonin level was elevated only in 1 patient with malignant lesions. Among ultrasonography findings, no significant statistical difference was found between the 2 groups with regard to number, dimensions, growth progression, or hypoechochogenic pattern of the nodules. Regarding scintigraphic findings, no significant difference was found between the 2 groups. However, a positive correlation (r = 0.90; P < 0.0001) was found between fine needle aspiration biopsy cytological findings and histological diagnoses. The sensitivity, specificity, and accuracy of fine needle aspiration biopsy were 95%, 86.3%, and 90.4%, respectively. A multiple regression analysis showed that only fine needle aspiration biopsy (β coefficient = 0.963; P < 0.0001) significantly contributed to detecting malignancy (multiple r = 0.973; P < 0.0001).

This study provides strong evidence that fine needle aspiration biopsy is a safe technique even in childhood and adolescence, offering the best sensitivity, specificity, and accuracy in detecting malignancy compared with conventional approaches. (J Clin Endocrinol Metab 86: 4644–4648, 2001)

Abbreviations: BL, Benign lesions; FNAB, fine needle aspiration biopsy; ML, malignant lesions; US, ultrasonography.
very low false negative and false positive rates, with accuracy ranging between 69% and 93% (13, 15). On the contrary, for children few data are available, and there are still many questions without unanimous or clear answers, such as, is FNAB a safe procedure for children? Some consider this procedure of limited usefulness in children because of its discomfort and the high rate of side-effects such as papillary endothelial hyperplasia, hemorrhage, vascular proliferation, vascular thrombosis, fibrosis, cystic change, infarction, and abscess (6–8, 15, 20). However, in our series most pediatric patients who underwent FNAB did not develop any complications, which agrees with other data (9, 17). Some researchers advocate surgery for the majority of children with solitary thyroid nodules (7). In our experience, considering only the cases with solitary thyroid nodules, we have seen a histological benign lesion in 13 of 27 submitted to surgery and a cytological benign lesion (obtained by FNAB) in 28. If we also consider the cases with 2 or more nodules, a histological benign lesion was found in 9 of 15 cases submitted to surgery and in 17 submitted only to FNAB. In conclusion, the frequency of malignant lesions was only 23% (20 of 87). Consequently, surgery is not recommended as the initial approach to thyroid nodules.

When is FNAB recommended? Some researchers recommend it only when nodules are palpable (21), because epidemiological reports rarely show thyroid cancer in impalpable nodules. Furthermore, to perform FNAB every time that a nodule is accidentally revealed by US would exaggerate the use of this procedure; in addition, the most frequent thyroid cancer in childhood and adolescence is the papillary type (10), which is usually a slow-growing tumor with a very indolent course even after local and pulmonary metastases have occurred (18). However, other researchers show that sometimes even nodules larger than 2 cm may be revealed only by US (22, 23). In fact, physical examination is relatively effective in detecting the nodules localized in the isthmus or in the anterior surface, but is much less so for the nodules localized in the upper pole of the gland, even if they are large. Moreover, thyroid cancer has been diagnosed even in very small nodules (22, 24, 25); in addition, some report that up to 10% of children with thyroid cancer may die of the disease, which is very worrisome (26, 27). Therefore, different researchers suggest different nodule cut-off dimensions to perform FNAB: more than 1 cm (28), 1.5 cm (14), or 2 cm (21). We think that other factors that derive from clinical history must be considered, such as previous external radiation for other malignancies of the head and the neck, family history of thyroid cancer, rapid nodule growth, ecographic characteristics, and suspicious cervical adenopathy.

In our series FNAB was performed in patients with both palpable and impalpable nodules. In these latter (six patients), nodule dimensions ranged from 0.8–1.5 cm, and we decided to perform FNAB precisely because other risk factors for malignancy were present: external radiation for leukemia in one patient, cervical adenopathy associated with subjective symptoms of neck compression in another, rapid spontaneous nodule growth in two patients, rapid growth of a nodule in one treated with L-T4, and suspicious isolated adenopathy in the last patient. The first four children had ML.

The main questions, however, are whether FNAB is the most useful procedure to detect malignancy, whether surgical treatment is needed, and whether this approach compares favorably with conventional clinical, laboratory, and imaging studies. In our series FNAB showed the highest sensitivity, specificity, and accuracy. On the contrary, some researchers report an accuracy lower than those of US and scintigraphy (17), but these data are probably due to small study groups. Other researchers show a correlation between FNAB reports and a histological diagnosis of 100% in a small cohort of patients (18). Furthermore, in our series no side-effects were recorded, which confirms that FNAB is a safe technique that clearly identifies nodules with malignant or suspicious cytology warranting surgery.

In our patients, signs and symptoms of neck compression were similar in the two groups, indicating that benign lesions (e.g. goiter) may lead to discomfort. On the contrary, the frequency of cervical adenopathy was significantly higher in thyroid cancer (78.9%), as noted by others (18, 29), confirming the importance of an accurate physical examination.

The only patient with a high serum calcitonin level was affected with medullary carcinoma (30). The association between autoimmune thyroiditis and thyroid carcinoma is still a matter of debate. We diagnosed papillary carcinoma in three cases with thyroid autoimmune diseases (one Graves’ disease and two thyroiditis), but this number is too small to determine an association in children (7, 10, 31, 32).

US revealed that most nodules were hypoechogenic lesions, both in the group with ML (58.7%) and in the group with BL (28.6%). We found this of limited value in detecting malignancy, because most hypoechogenic nodules are benign. Moreover, hyperechogenic lesions do not exclude malignancy, so none of US-revealed features are sufficiently specific to guide the selection of patients affected by thyroid cancer (33–35). Also, evaluation of thyroid nodules with color Doppler sonography has not given any specific patterns for malignancy (36). US also identifies the number, dimensions, and progressive growth of nodules. We found that the number of nodules was not related to malignancy, and in particular, the solitary nodule was not significantly more likely to be malignant, but this remains controversial (3–5, 18, 37).

Nodule dimensions were not related to malignancy in our patients: 55% of children with ML had a malignant nodule with a diameter less than 2 cm, as reported by others (22, 25). On the contrary, adult series report a higher frequency of thyroid cancer in nodules larger than 4 cm (38). Progressive growth was present in 57% of our group with BL and in 72% of the group with ML. Although this is usually considered predictive of malignancy, it was not so in our patients, three of whom with BL, treated with L-T4, had progressive growth. These findings confirm previous observations describing poor correlation between progressive growth and nodule histology in both adults and children (6, 39).

Thyroid scintiscanning has long been considered the first examination to perform on a thyroid nodule. However, in recent years it has been less frequently used in the initial routine evaluation because most benign and malignant nodules show reduced concentrations of radioisotope, whereas hyperfunctional nodules are occasionally malignant (6, 11, 39).
ARTICLE

Thyroid Nodules and Cancer in Children and Adolescents Affected by Autoimmune Thyroiditis

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Objective: To investigate the association between juvenile autoimmune thyroiditis (JAT) and thyroid cancer in pediatric patients.

Design: We conducted a retrospective study among children and adolescents affected by JAT.

Settings: Data from 6 Italian pediatric endocrinology centers were collected.

Participants: Three hundred sixty-five children and adolescents affected by JAT diagnosed at 3.6 to 17.0 years of age.

Interventions: All patients underwent clinical examination and thyroid function test every 6 to 12 months and thyroid echography every 12 to 24 months. Fine-needle aspiration biopsy was performed in 39 patients with nodule diameter of 1 cm or larger, as well as in 4 patients with nodule diameter of less than 1 cm and echographic findings suspicious for neoplasm. Twenty-three patients underwent surgery.

Main Outcome Measures: Thyroid function, echographic pattern, nodule diameter, the presence of lymphadenopathy, and cytologic and histologic diagnoses were considered.

Results: Thyroid nodules were found in 115 patients; findings in 11 of these were consistent with papillary carcinoma, with 5 exhibiting lymph node metastasis. The prevalence of male sex among patients with cancer was greater than that among patients with JAT (odds ratio [OR], 2.95; 95% confidence interval [CI], 1.44-6.20). The growth of nodules during levothyroxine sodium therapy (OR, 15.60; 95% CI, 1.87-181.90) and the finding of lymphadenopathy (OR, 5.44; 95% CI, 1.05-30.50) were statistically significantly associated with the presence of cancer, while uninodularity and hypoechogenicity were not.

Conclusions: The observed prevalences of thyroid nodules and thyroid cancer in our JAT case series were 31.5% and 3.0%, respectively. Papillary carcinoma was the only histotype detected. The finding of lymphadenopathy, a lack of response to levothyroxine therapy, and nodule hypoechogenicity suggested malignancy. Fine-needle aspiration biopsy was reliable in selecting patients for referral to surgery.

Arch Pediatr Adolesc Med. 2008;162(6):526-531

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We conducted a retrospective study among 365 children and adolescents (308 female and 57 male) diagnosed as having JAT at 3.6 to 17.0 years of age. The JAT diagnosis was based on positive findings of antithyroid antibodies and a dishomogeneous hypoechoic ultrasound pattern. None of the patients were affected by chromosomopathy or underwent radiation therapy for a neoplasm involving thyroid fields. All patients had been followed up for at least 1 year (mean [SD] follow-up period, 4.7 [3.9] years) except for 3 patients in whom cancer discovery and JAT diagnosis coincided. The study involved 6 Italian pediatric endocrinology centers that provided data on consecutive patients in whom a JAT diagnosis was made between January 1997 and April 2006. Patients were diagnosed as having JAT based on the following clinical findings: goiter (290 patients), signs or symptoms of hypothyroidism (48 patients) or thyrotoxicosis (11 patients), visible or palpable nodule (11 patients), and family history of thyroid diseases or autoimmune disease (5 patients).

At JAT diagnosis, 96 patients (26.3%) were prepubertal, and 269 patients (73.7%) were pubertal. When initially seen, 195 patients (53.4%) had euthyroidism, 139 patients (43.6%) had hypothyroidism, and 11 patients (3.0%) had thyrotoxicosis. Among the patients with euthyroidism, 192 had goiter, and 3 had a family history of thyroid diseases or autoimmune disease. Clinical examination and assessment of thyroid function were performed every 6 to 12 months. Thyroid echography was performed every 12 to 24 months and every 6 to 12 months in patients with a suspicious thyroid nodule.

We reported the finding of lymphadenopathy, the thyroid function at nodule discovery, the number of patients with nodular disease (specifying patient sex and age), the echographic pattern (echogenicity, nodule diameter, and uninnodular or multinodular disease), and the numbers of patients who underwent fine-needle aspiration biopsy (FNAB) for cytologic study and subsequent surgery. In patients who received levothyroxine sodium treatment before cancer diagnosis, we investigated the change in nodule diameter. In patients with thyroid cancer, we considered the thyroid function at cancer detection; the histologic diagnosis of the surgical specimen; the timing of JAT, nodule, and cancer detection; the correlation between cytologic and histologic findings; and the cytologic diagnosis based on FNAB findings (except for 5 patients who directly underwent surgery because of symptoms of compression on adjacent organs or because of echographic features of a lymph node suspicious for malignancy).

We also compared the following characteristics in patients with thyroid cancer vs patients with a benign nodule (defined by cytologic or histologic findings): sex, age at nodule discovery, nodule hypoechochogenicity, age at diagnosis of thyroiditis, changes in nodule diameter during levothyroxine therapy, prevalence of uninnodular and multinodular disease, and prevalence of clinically detectable lymphadenopathy. The Fisher exact test and t test were used to compare these variables.

Thyroid nodules were found in 115 of 365 patients with JAT (31.5%), 69 (60.0%) of whom had a solitary nodule and 46 (40.0%) of whom had multiple nodules. Thirty-eight nodules were palpable at clinical examination, and the presence of all of them was confirmed by echography. At diagnosis, the patient age range was 8.5 to 18.0 years, and the size range of the single or dominant nodule was 0.3 to 3.0 cm. Figure 1 shows the timing of nodule discovery relative to JAT diagnosis.

Of 52 patients in whom a nodule was present at JAT diagnosis, 26 (50.0%) had euthyroidism, 25 (48.1%) had hypothyroidism, and 1 (1.9%) had thyrotoxicosis. Of 63 patients in whom a nodule was detected 0.5 to 6.9 years following JAT diagnosis, 55 (87.3%) had euthyroidism, 20 (31.7%) had received levothyroxine therapy, and 8 (12.7%) had hypothyroidism.

Figure 2 shows the numbers of patients with thyroid nodules, the numbers of patients who underwent FNAB and surgery, and the numbers of patients with papillary carcinoma. Four patients with a nodule diameter of less than 1 cm underwent FNAB on the basis of clinical and echographic findings suggestive of cancer (rapid increase in nodule diameter or echographic features of a lymph node suspicious for malignancy), and 1 was found to have papillary carcinoma. Among 35 patients with a cytologic diagnosis of a benign lesion, 10 patients underwent surgery, 1 of whom was found to have papillary carcinoma. Among the 10 patients, 3 were referred for surgery because of clinical evidence of persistent lymphadenopathy with a hypoechoic nodule, 3 were referred because of cosmetic or discomfort concerns or the presence of compression symptoms (cough, dysphagia, or upper airway obstruction), and 4 were referred because of persistent growth of the nodule (despite irregular margins of the lesion, high intranodular Dop-
cancer in JAT, but it contrasts with other studies that report a lower frequency of papillary carcinoma compared with other types of histologically determined lesions. 5,8,21-26 There are well-documented cases affected by follicular lesions and undifferentiated and squamous cell carcinomas. 5,8,21,22 Unlike other studies,23-26 we found no cases of lymphoma in our series.

Among our patients, the diagnostic accuracy of FNAB in differentiating benign from malignant nodules in JAT was high and was in agreement with the rates reported by some investigators,6,12,21 and was higher than rates reported by others. 5,8,24 This suggests that in our series FNAB had a high predictive value that permitted patients to be appropriately selected for referral to surgery. However, surgery was performed in 10 patients with a cytologically benign lesion for symptoms of compression on adjacent organs, an increase in nodule diameter during levothyroxine therapy, or echographic features of a nodule or lymph node that were strongly suggestive of malignancy. In 9 patients, histologic examination confirmed the presence of a benign lesion; in the patient in whom cytologic examination revealed Hashimoto thyroiditis, a papillary carcinoma was detected. The discrepancy between cytologic and histologic findings has been discussed elsewhere.5,24

A comparison of data among 11 patients with papillary carcinoma vs 37 patients with cytologically or histologically confirmed benign lesions was notable relative to the finding of lymphadenopathy and the increases noted in nodule diameter during levothyroxine therapy. The finding of lymphadenopathy confirms the importance of clinical examination given that thyroid cancer in children is characterized by locoregional lymphadenopathy in 35% to 83% of cases, which is much higher than in adults.11,27 Papillary carcinoma has a marked tendency to early lymph node metastasis; it is estimated that about half of the patients with papillary carcinoma have cervicofacial lymphadenopathy.3 Based on findings among children with nodular disease, including those unaffected by IAT, the presence of lymphadenopathy ranks second after FNAB in accurate detection of malignancy.28

The therapeutic efficacy of reducing a thyroid nodule diameter in thyroiditis has rarely been studied, although some investigators claim that a lack of reduction in nodule diameter during levothyroxine therapy is prognostic of a malignant nature of the nodule.21,29,30 Evidence for this claim seems to be statistically confirmed by our study, which showed that levothyroxine therapy reduced nodule diameters in 0 of 8 treated patients affected by cancer but in 15 of 26 patients (57.7%) without cancer.

A comparison between 11 patients with papillary carcinoma and 37 patients with benign lesions showed that thyroid function, patient sex and age, the number of nodules, and a hypoechogenic ultrasound pattern were similar in the 2 groups. That the hypoechogenic ultrasound pattern was similar is linked to its low specificity (ie, the high prevalence of hypoechogenic nodules in benign lesions). However, 8 of 11 patients with a malignant neoplasm had a hypoechogenic lesion, which is known to be suspicious for cancer.6,31

The presence of a solitary nodule is generally considered suspicious for malignancy. However, echography of ten reveals multinodularity vs uninnodularity on clinical examination. The finding of multiple nodules on echography carries a greater risk of cancer compared with the finding of a solitary nodule.6,31 The discovery of multiple nodules also carries greater risk, in that 7 of 11 patients in our series with cancer had at least 2 nodules on echography, which was higher than reported by other investigators.5

Regarding the male-female ratio, more girls were affected in our series, as reported by other authors.27,32,33 However, more boys were affected among patients with thyroid cancer compared with the entire JAT case series. Thyroid function was not found to be a risk factor for developing cancer. This contrasts with findings reported by other investigators,30,34 who claim that chronically elevated thyroid-stimulating hormone levels stimulate the growth of thyroid tissue, leading to the formation of nodules and thyroid cancer.

Another consideration is thyroglobulin level measurement in the washout fluid from FNAB of neck lymph nodes. This protocol, previously used for early detection of cervical metastases following thyroidectomy and radioiodine therapy, also detects lymph node metastasis before surgery.5,36 In 1 of 2 patients in our series who underwent this procedure, it proved particularly useful in that it permitted detection of a malignant lesion in a patient in whom the cytologic findings were benign.

CONCLUSIONS

To our knowledge, this is the first study to analyze the relationship between JAT, cancer, and thyroid nodules in a large case series of pediatric patients. Our results carry the limitation of a retrospective study design and may provide an imprecise estimate of the occurrence of thyroid nodules and cancer in patients affected by JAT. However, our data show that thyroid nodular disease is present in 31.5% of pediatric patients with JAT and that cancer occurs among these in at least 9.6% of cases, with papillary carcinoma being the most common histologic type.

The finding of lymphadenopathy and increases in nodule diameter during levothyroxine therapy are 2 factors that are statistically significantly more frequent in patients with thyroid cancer than in patients with a benign lesion. Thyroid echography provides further useful diagnostic information. Among patients with thyroid cancer, hypoechogenicity seems to predominate over other ultrasound patterns, although it is common also in benign nodules. Furthermore, multinodularity is more frequent than uninnodularity in patients with cancer. Finally, the accuracy of FNAB supports its diagnostic usefulness in the management of patients with thyroid nodules and in the differentiation between benign and malignant lesions.

Accepted for Publication: December 7, 2007.

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Thyroid function was not found to be a risk factor for cancer in JAT, but it contrasts with other studies that report a lower frequency of papillary carcinoma compared with other types of histologically determined lesions.\textsuperscript{5,8,21-26} There are well-documented cases affected by follicular lesions and undifferentiated and squamous cell carcinomas.\textsuperscript{5,8,21,22} Unlike other studies,\textsuperscript{23-26} we found no cases of lymphoma in our series.

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Financial Disclosure: None reported.

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Statistical analysis: Corrias, Cassio, and Mussa.

Administrative, technical, and material support: Corrias, Cassio, Weber, Mussa, Wasniewska, Rapa, Gastaldi, Einaudi, Baronio, Vigone, Messina, Bal, Bona, and de Sanctis.


Financial Disclosure: None reported.

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Multivariate Analysis of Clinicopathologic Parameters for the Insular Subtype of Differentiated Thyroid Carcinoma

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Hypothesis: Insular carcinoma represents a more aggressive subtype of differentiated thyroid cancer on multivariate analysis after controlling for various clinicopathologic parameters.

Design: Retrospective analysis.

Setting: Tertiary referral center at a university hospital.

Patients: One hundred twenty-seven consecutive patients having a histological diagnosis of the follicular variant of papillary thyroid carcinoma or follicular thyroid carcinoma.

Main Outcome Measure: A logistic regression model was used to examine the relationship between various clinicopathologic parameters and the insular subtype.

Results: The insular subtype involved 14 of 127 tumors. Unlike extrathyroidal extension and nodal metastasis, primary tumor diameter (>40 mm vs ≤40 mm; P = .008) and distant metastasis (P = .003) correlated with the insular subtype. Both parameters were interrelated since tumors greater than 40 mm displayed distant metastasis more often (30% vs 8%; P = .008) than tumors measuring 40 mm or less.

Conclusions: These findings suggest that an unidentified somatic event may induce an accelerated proliferation of the transformed thyrocytes, which may ultimately result in enhanced rates of distant metastasis with increasing tumor volume.

Arch Surg. 2001;136:941-944

Since the seminal description of insular carcinoma by Carcangiu et al in 1984,1 no universal consensus has been reached as to the biological aggressiveness and prognostic relevance of this comparatively rare subtype of thyroid cancer. Some authors have identified significant correlations between insular carcinoma and the occurrences of extrathyroidal growth and nodal metastases.2 These observations are awaiting confirmation by investigations that include an unselected noninsular control group. Many literature reports in this field have been hampered by the lack of such a noninsular control group. Because of the rarity of insular carcinoma—accounting for only 3.8% (27/720) to 6.2% (41/657) of thyroid tumors1-3—recruiting enough patients with insular carcinoma has posed difficult problems.

More recent publications have addressed the issue of biological aggressiveness by comparing patients with insular carcinoma with control groups composed of patients with more invasive forms of differentiated thyroid carcinoma. These controls have had neoplasms as diverse as widely invasive follicular carcinoma,5,7 the tall cell, and diffuse sclerosing variants of papillary carcinoma.5,6 Owing to the unavailability of an unselected noninsular control group, this approach does not allow one to draw definitive conclusions about the unique oncological properties of the insular subtype. To resolve the issue of biological aggressiveness of insular carcinoma, our institutional investigation was conducted in an unselected cohort of 127 consecutive patients with differentiated thyroid cancer.

See Invited Critique at end of article

RESULTS

UNIVARIATE ANALYSES OF CLINICOPATHOLOGIC PARAMETERS GROUPED BY OPERATIVE STATUS

A total of 14 (5 FVPTCs, 9 FTCs) insular tumors (11%) were identified among the 127 patients with FVPTC and FTC (Table 1). Of these, 7 were both primary...
SOMATIC MUTATIONS IN INSULAR CARCINOMA

The role of these hypothesized genetic events in the unique growth pattern and metastatic potential of insular carcinoma remains to be ascertained. Potential candidate genes for such somatic events are the ras gene family or the p53 gene. In 5 of 8 cases of insular carcinomas and also in widely invasive FTC, somatic point mutations were detected in the H-RAS and N-RAS histotypes by single-strand conformation polymorphism analysis following amplification by polymerase chain reaction. Intriguingly, 3 of the 5 ras mutations identified in insular carcinoma involved the CAA→AAA transversion at codon 61 (glutamyl transpeptidase domain) of the N-RAS gene. Transversion mutations (substitution of a purine for a pyrimidine or vice versa) obviously predominate in undifferentiated thyroid tumors as opposed to transition mutations (substitution of a purine for a purine or a pyrimidine for a pyrimidine), which prevail in differentiated thyroid carcinomas. In follicular, poorly differentiated, and undifferentiated thyroid carcinomas, point mutations in the ras oncogene were significantly associated with the appearance of hematogenous metastases (40% vs 6%; \( P = .03 \)) and bone metastases (54% vs 5%; \( P = .003 \)) on univariate analysis. This observation suggests a role of ras gene activation in the process of distant metastasis. Molecular analysis of exons 5, 6, 7, and 8 of the p53 gene revealed that 14 of 46 insular carcinomas harbored somatic mutations in these exons. Considering these molecular data and the current clinicopathologic findings, insular carcinoma seems to represent a subtype rather than an entity in its own right within the spectrum of thyroid tumors. In agreement with this interpretation is the recent view that the insular subtype represents a higher grade of an existing thyroid carcinoma. The poorer survival rates in insular carcinoma are accounted for by the significant correlation we found between insular carcinoma and distant metastasis. This finding underscores the importance of having an unselected control group and of controlling for primary tumor size and the T, N, and M categories.

CLINICAL IMPLICATIONS

The surgical strategy for insular carcinoma should aim at achieving local control. To this end, a systematic dissection of the cervicocentral lymph nodes is advocated, since approximately half of insular carcinoma cases display nodal metastases by the time of diagnosis according to the literature and our data (Table 1). In

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Table 1. Univariate Analysis of Clinicopathological Parameters Grouped by Operative Status

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients</th>
<th>OR (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>T classification, % ‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>20</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>36</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>4</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>40</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Median tumor diameter, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(25%-75% quartiles)</td>
<td>22 (13-30)</td>
<td>60 (53-64)</td>
<td>( .003 )</td>
</tr>
<tr>
<td>Nodal metastasis (N1 vs N0)</td>
<td>20</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Distant metastasis (M1 vs M0)</td>
<td>36</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Tumor entity (FVPTC vs FTC)</td>
<td>40</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

*OR indicates odds ratio; CI, confidence interval; FVPTC, follicular variant of papillary thyroid carcinoma; FTC, follicular thyroid carcinoma.
†Excluding 24 patients with missing information on primary tumor diameter.
‡Tumor classification according to the International Union Against Cancer.
§Including pulmonary M1 diagnosed by postoperative scintigraphy.
Pathogenesis, diagnosis and management of thyroid nodules in children

M Niedziela

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(Requests for offprints should be addressed to M Niedziela; Email: mniedzie@am.poznan.pl)

Abstract

According to the literature thyroid nodules are quite rare in the first two decades of life. However, there are some exceptions, relating to areas with an iodine deficiency or affected by radioactive fallout, where the risk of nodules and carcinomas is increased. Therefore, it is a great challenge for the physician to distinguish between benign and malignant lesions preoperatively, and not only in these areas of greater risk. A careful work-up, comprising the patient’s history, clinical examination, laboratory tests, thyroid ultrasound, scintigraphy, fine-needle aspiration biopsy (FNAB) and molecular studies, is mandatory to improve the preoperative diagnosis. The differential diagnosis should also include benign thyroid conditions such as: (i) congenital hypothyroidism due to dyshormonogenesis or ectopy, (ii) thyroid hemiagenesis, (iii) thyroglossal duct cyst, (iv) simple goiter, (v) cystic lesion, (vi) nodular hyperplasia, (vii) follicular adenoma, (viii) Graves’ disease and (ix) Hashimoto thyroiditis, all of which can predispose to the development of thyroid nodules. The majority of thyroid carcinomas derive from the follicular cell (papillary, follicular, insular and undifferentiated (or anaplastic) thyroid carcinoma), whereas medullary thyroid carcinoma derives from calcitonin-producing cells. Inherited forms of thyroid cancer may occur, especially in relation to medullary thyroid carcinoma. FNAB is a critical factor in establishing the preoperative diagnosis. However, we should keep in mind the fact that a conventional cytological evaluation can miss the neoplastic nature of a lesion and the employment of immunocytochemical and molecular studies of aspirates from FNAB can give us a more precise diagnosis of neoplasia in thyroid nodules once they are detected.

Introduction

Thyroid nodules are uncommon in children before puberty (1.5% or less) (Kirkland et al. 1973, Rallison et al. 1975, Scott & Crawford 1976, Yip et al. 1994, Millman & Pellitteri 1997). Any nodule discovered in such an age group should therefore be viewed with suspicion and the diagnostic approach should be more aggressive in children than in adults (Scott & Crawford 1976, Silverman et al. 1979, Ridgway 1991) because they are more often malignant than in adults (Belfiore et al. 1989). The mean incidence of thyroid carcinomas in childhood thyroid nodules which were operated on is summarized in Table 1 and shows an overall 26.4% risk of cancer.

The sex distribution in a group of all-adult patients with thyroid carcinoma is different from that in children. In adults, women outnumber men 4:1, whereas in children below 15 the ratio of girls to boys is 1.5:1 and in patients aged 15–20 the female/male ratio is 3:1 (Attie 1996). The available data show that males and children under 10 years are at higher risk of cancer, and this is in agreement with data from other authors (Yip et al. 1994). Age is also the major determinant of recurrence in pediatric differentiated thyroid carcinoma, particularly in those younger than 10 years (Alessandri et al. 2000, Jarzab et al. 2005).

Thyroid nodular disease (TND) comprises a wide spectrum of disorders including a solitary nodule, multinodular goiter (MNG), nodular goiter observed in autoimmune thyroid disease (AITD), i.e. chronic lymphocytic thyroiditis (Hashimoto thyroiditis (HT)) or Graves’ disease (GD) and also occurring in the form of nonpalpable thyroid nodules. In
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Endocrine-Related Cancer (2006) 13 427–453

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Endocrine-Related Cancer (2006) 13 427–453
1351-0088/06/013–427 © 2006 Society for Endocrinology Printed in Great Britain

DOI:10.1677/erc.1.00882
Online version via http://www.endocrinology-journals.org
without crossing its border, or (iv) the presence of a neoplastic lesion within the capsule (Rosai et al. 1992, Niedziela 2002). Recently the Chernobyl Pathologists Group suggested that tumors with ‘borderline’ features, should be classified either as ‘a well-differentiated tumor of uncertain malignant potential (WDT-UMP)’ if they exhibit questionable PTC-type nuclear changes, with or without questionable capsular penetration, or as ‘a follicular tumor of uncertain malignant potential (FT-UMP)’ if they show questionable capsular penetration without nuclear changes (Williams 2000, Hirokawa et al. 2002, Papotti et al. 2004). Complicated historical descriptions, such as those above, should alert the clinician to the need for careful clinical follow-up, because the behavior of thyrocytes remaining after partial thyroidectomy is unpredictable. This problem is significant since these thyroid tumors occur at such an early age and consequently the life-long prognosis is difficult to determine. In our population of children this type of thyroid tumor was quite frequent and I prefer them to be treated (after surgery) as benign lesions, i.e. with L-T4 supplementation to maintain a normal TSH level, but to be just as careful and alert to change as in malignant lesions (Niedziela 2002). Abnormal thyroid growth appears to be complex, depending on many factors, especially TSH. However, the process is initiated without TSH stimulation in the majority of neoplastic thyroid tumors.

**Thyroid carcinoma in the course of GD**

The various approaches to GD designed to avoid progression to neoplasia are surgery vs radioiodine vs antithyroid drugs (ATDs) (Rivkees et al. 1998, Kraiem & Newfield 2001). It is well known that long-term treatment of GD with ATDs can predispose to further development of a malignant lesion within the enlarged thyroid (Dobyns et al. 1974). Palpable nodules in our young patients with GD were diagnosed as PTCs (Fig. 2H) (Niedziela & Korman 2002, 2003). It is possible that the relatively higher iodine intake from a prophylaxis program was responsible for these two different disorders (GD and thyroid carcinoma) involving two independent pathogenetic links.

**Thyroid carcinoma in the course of chronic lymphocytic autoimmune thyroiditis (HT type)**

HT type thyroiditis, unlike the atrophic type, is usually manifested by a goiter with increased firmness of the whole gland on palpation, usually in a diffuse form but occasionally in a focal form.

Based on data in the literature, autoimmune thyroiditis is considered to be a condition preventing the expansion of a neoplasm (Loh et al. 1999). A nodule in HT may progress to carcinoma, especially PTC, but it can also be associated with a benign neoplasm. **Iodine prophylaxis in a previously iodine-deficient area and its relative excess in the diet should be considered as responsible for both HT and carcinoma** (Bravermann 1994, Franceschi 1998, Stanbury et al. 1998, Feldt-Rasmussen 2001, Niedziela & Korman 2003). In several of our patients with HT we detected thyroid neoplasms, both benign FAs (Fig. 2I) and carcinomas (only PTC) (Fig. 2J) at the time of HT confirmation (Niedziela & Korman 2003). These findings therefore do not support the so-called ‘protective role’ of thyroiditis (Loh et al. 1999).

The question arises as to whether the thyroiditis preceded the nodule or vice versa. New data coming from molecular studies of the BRAF mutations, the molecular marker of PTC, indicate that the detection of activated mutation of this gene in a patient with a prior HT may be helpful in predicting progress to PTC, even in the absence of a palpable nodule (Kim et al. 2005). Long-term follow-up may help us in the further identification of true-positive risk factors for neoplasia.

In all our patients with thyroid neoplasms the diagnosis ofAITD was established at the time of TND evaluation and, in the case of GD, before the introduction of ATDs. To date, no direct link has been proved but it is suggested, in the literature, that a solitary nodule (or nodules) in the course of GD may lead to quite an aggressive cancer (Rieger et al. 1989, Pellegriti et al. 1998), whereas in HT the nodule may appear as an cancer, either in an occult form or as a lymphoma (Loh et al. 1999).

Both types of AITD should be viewed with suspicion and more established forms of treatment should be applied much earlier (e.g. in the form of radioiodine if the GD is still active even with treatment (i.e. if showing a hypoechogenic pattern of the gland and an elevated titer of thyroid-stimulating hormone receptor antibodies (TRAb)) or surgery if a coexisting nodule or nodules are present).

I believe that both AITDs predispose to nodules but the risk of cancer developing is difficult to forecast. Since patients in the AITD group are at risk of developing thyroid neoplasia in the future, long-term follow-up is essential, especially in areas with a relatively higher intake of iodine in the diet.
indicating thyroid cancer, are present (e.g. PTC (Fig. 6C) or MTC (Fig. 6D)) then total thyroidectomy with elective central lymph node removal is obligatory (Polish Guidelines 2001). If the material obtained from the thyroid nodule is insufficient for diagnosis then a second biopsy is recommended.

Overall, FNAB is the most reliable and cost-effective method of distinguishing benign from suspicious or malignant thyroid nodules (Castro & Gharib 2003).

**Interpretation of FNAB**

PTC, the most common type of thyroid cancer, as well as medullary and anaplastic thyroid carcinoma, may be diagnosed preoperatively from cytological examination of biopsy material. It is necessary here to mention some aspects of false-positive results for malignancy in conventional cytology in some clinical conditions. One of these is HT in the hypothyroid phase, whether clinical or subclinical. Normalization of TSH is mandatory, prior to FNAB, because if it is elevated, it promotes goiter development and could be responsible for morphological changes in epithelial follicular cells.

If nodules are not present then L-T4 therapy is recommended, before FNAB, to normalize the TSH level, which in turn normalizes the stimulation of thyroid epithelial cells. Otherwise the resulting overstimulated follicular cells may lead to a false-positive result at cytology, with nuclear grooves and other features suggesting PTC (Kini 1996, Gould et al. 1989, Chhieng et al. 1997). A careful clinical follow-up 4–6 weeks later and a subsequent visit, which should include an US check, after a 3 month interval, is advisable to avoid unnecessary thyroidectomy. If, with this correction based on clinical and US examinations, there is still a need for a FNAB then it should be directed to the most suspect area within the thyroid, i.e. to a detected nodular region. FNAB should be performed directly if a solitary palpable lesion is present (Fig. 2J) or if a suspected hypoechogenic area is detected with US (Fig. 2J). The effects of ATDs given before FNAB should also be considered in the interpretation of biopsy specimens, otherwise the cytological conclusion may be inaccurate.

An adequate (true-positive) diagnosis can be made in more than 90% of undifferentiated, medullary and papillary carcinomas using FNAB (Kini 1996). An FTC cannot be distinguished preoperatively by FNAB from a hyperplastic nodule, an FA or a follicular variant of PTC (Kini 1996, Hamburger 1994). Ardito et al. (2001) concluded that the preoperative work-up of children and adolescents with thyroid nodules requires FNAB as the initial diagnostic test, since malignancy was detected in 73.3% of their lesions, prior to surgery. Zimmermann (1997) noted a false-negative result from biopsy in only 2% of his aspirates. Corrias et al. (2001) found a high degree of sensitivity (95%), specificity (86.3%) and accuracy (90.4%) of FNAB in relation to histological diagnosis and they therefore also advocate the use of this method as a diagnostic test in euthyroid patients with thyroid nodule(s). Raab et al. (1995) stated that FNAB is useful in the management of pediatric thyroid nodules because of its high diagnostic accuracy and minimal invasiveness. Arda et al. (2001) assert that surgery should only be performed in patients with malignant or suspicious cells and that it has no place in patients whose previous FNAB revealed benign cells. All the patients with suspicious or malignant FNAB results in our series were found to have adenomas or carcinomas postoperatively. However, cancer was also detected in tumors with a benign preoperative cytology (Niedziela 2002).

As there is therefore a risk of false-negative cytological results with earlier methods of investigation, including FNAB cytological examination, a more accurate preoperative diagnostic test is still required in TND (Haugen et al. 2002, Bojunga & Zeuzem 2004).

**Molecular studies employed for the detection of malignancy**

Each FNAB aspirate, in parallel with conventional cytological evaluation, may be subjected to RT-PCR in the search for the expression of different neoplastic markers within the aspirated cells (Gasbarri et al. 1999, Russo et al. 1999, Takano et al. 1999, Takano & Amino 2002).

These markers include telomerase (Haugen et al. 1997), Hector Baltifora Mesothelial cell (HBME-1) (Sack et al. 1997), galectin-3 (Gasbarri et al. 1999, Bartolazzi et al. 2001, Saggiorato et al. 2001, Kovacs et al. 2003), CD44v6 (Gasbarri et al. 1999) and cytokeratin-19 (Khurana et al. 2003). However, these do not provide a precise identification of the various thyroid cancer subtypes. Some markers have also been detected in PTC (ret/PTC translocations (Cheung et al. 2001), platelet-derived growth factor (Yano et al. 2004)) and FTC (PAX8-PPARγ1 (Kroll et al. 2000)). Additionally,
Papillary Thyroid Carcinoma
An Overview
(Arch Pathol Lab Med. 2006;130:1057–1062)

Nabeel Al-Brahim, MD; Sylvia L. Asa MD, PhD

Papillary thyroid carcinoma is the most common malignant tumor of the thyroid. It has a variable macroscopic appearance that differs according to the variant microscopic morphologies and the presence or absence of degenerative changes. The histologic variants can be challenging to the pathologist, and some are of clinical significance because of prognostic implications. In this short review, we discuss an approach to papillary carcinoma, the diagnostic dilemmas and controversies, and the ancillary studies that are helpful in resolving them, including immunohistochemistry and molecular studies.

(Arch Pathol Lab Med. 2006;130:1057–1062)

Thyroid cancer is the most common endocrine malignancy and represents 1% of all malignancies. It is also the most rapidly increasing cancer in women. In 2004, approximately 26,000 new cases of thyroid cancer were recorded in the United States, 75% of them in female patients, and thyroid cancer represented the eighth most common cancer in women. 1 Papillary thyroid carcinoma (PTC) is the most common malignant tumor among all thyroid cancers, comprising an estimated 80% of thyroid cancers. 2 In contrast to the high incidence, death from thyroid cancers, comprising an estimated 80% of thyroid cancers.

There are several established risk factors for PTC, including genetic factors, ionizing radiation, and nodular disease of the thyroid. Several genetic syndromes predispose patients to thyroid cancer. Patients with familial adenomatous polyposis develop PTC, usually with distinctive morphologic findings. 3 In Cowden syndrome, patients commonly develop follicular lesion of thyroid, but PTC is also on record with this syndrome. 4 There is also emerging evidence for familial PTC, but the genetic basis of this disorder is as yet unknown. 5

Several molecular changes are known to underlie PTC, and these are of diagnostic as well as potential prognostic and/or therapeutic significance.

CLINICAL FEATURES

Papillary thyroid carcinoma has diverse clinical presentations. Most commonly it presents as a thyroid nodule that is discovered incidentally or on routine examination. Rarely, patients present with metastasis in a neck lymph node or with hoarseness of voice caused by involvement of the recurrent laryngeal nerve. Distant metastasis as a primary presentation is an exceptionally unusual finding.

The investigation of a thyroid nodule commonly includes ultrasonography imaging, nuclear scan, and fine-needle aspiration biopsy. The ultrasound is a useful test to distinguish solid from cystic lesions and to identify calcifications. Reading et al 6 reviewed ultrasonographic patterns that are conventionally applied to distinguish benign from malignant thyroid nodules. Among these patterns, 2 are characteristic of PTC. The first pattern is the presence of a solid, hypoechoic nodule with discrete echogenic foci. This diagnosis is further supported by the presence of microcalcification. The second pattern is the solid, hypoechoic nodule with coarse echogenic foci. On nuclear scan, papillary carcinoma is commonly a "cold" nodule; rarely, though, PTC can be a "hot" nodule. It is important to note that uptake of technetium is more common than uptake of iodine, and only the latter predicts a hyperfunctioning lesion associated with suppressed thyrotropin and increased thyroid function.

Fine-needle aspiration biopsy is the single most useful tool in the diagnosis of papillary carcinoma. Fine-needle aspiration biopsy has very high accuracy that reaches more than 95% in satisfactory specimens. 7 The cytologic morphology of PTC is characterized by a cellular aspirate in which the cells are arranged in monolayer sheets of cells, sometimes forming papillae and occasionally having psammoma bodies. The nuclear morphology is characterized by enlarged, overlapped nuclei with powdery chromatin and multiple micronucleoli. The majority of the nuclei have intranuclear grooves. Intranuclear inclusions can be seen.

GROSS PATHOLOGY

A critical component of thyroid diagnosis involves proper handling of thyroid specimens. It is important to distinguish a lobectomy specimen from a hemithyroidectomy specimen that includes the isthmus as well as the lobe. A subtotal thyroidectomy resection includes the lobe containing a dominant lesion, the isthmus, and a significant portion of the other lobe. It can be difficult for the pathologist to distinguish this type of specimen from a
total thyroidectomy. In some cases, the gland will be accompanied by a neck dissection specimen that may include the superior mediastinal contents. When the specimen is received, the different parts should be identified and all parts should be measured and weighed. The external surface is examined for the presence of adhesions, adherent or involved skeletal muscle, and parathyroid glands. The surface should be marked with india ink to determine resection margin involvement by tumor, but there is little rationale for identifying specific margins. The lobes should be serially sectioned from superior to inferior in approximately 0.3-cm-thick sections and examined carefully. The isthmus should be sectioned in the sagittal plane. The thyroid parenchyma should be examined for nodules and cysts. The following features should be documented: multiplicity, circumscription, size, consistency, and color. There is no specific rule for submission of sections; however, if the specimen is small, it can be submitted in toto. If the specimen is too large to do so, representative sections should be taken with consideration of the capsule of the lesion, which is required for evaluation in follicular lesions to determine malignancy.

Papillary carcinoma has different macroscopic morphologies. It may be solid or cystic with papillary excrescences in the classic variant. Solid nodules usually have a tan color and a firm consistency. The oncocytic variant has brown-to-mahogany color. The border of the nodule may be infiltrative or well circumscribed, with or without a capsule, and calcification may be seen. Sclerosis may be a prominent feature. Focal degenerative changes may occur either spontaneously or as a result of previous fine-needle aspiration. These changes include cystic formation, hemorrhage, or necrosis. Therefore, care should be taken when sampling these tumors to consider the periphery of the lesions because they are less prone to degenerative changes.

Multifocal papillary carcinoma appears macroscopically as multiple distinct nodules that are distributed throughout the entire thyroid. Care must be taken in handling such tumors as the measurement of the dominant nodule should be recorded. The appearance is determined by the underlying variant.

HISTOPATHOLOGY AND VARIANTS

The diagnosis of papillary carcinoma is based on nuclear morphology of a thyroid neoplasm. The existence of multiple architectural variants proves the irrelevance of architecture. The diagnostic nuclear morphology is characterized by the following constellation of features as seen in Figure 1:

1. enlarged and elongated nuclei with crowding and overlap;
2. irregular nuclear contour;
3. chromatin clearing with peripheral margination of chromatin, giving rise to what has been described as Orphan Annie Eye nuclei;
4. multiple micronucleoli located immediately underneath the nuclear membrane;
5. nuclear grooves resulting from irregularity of nuclear contour seen in 2 dimensions;
6. intranuclear cytoplasmic pseudoinclusions from the accumulation of cytoplasm in prominent nuclear grooves.

These features determine the diagnosis. Even in the presence of true papilla formation, lesions that lack the...
There is no prognostic significance attributed to these variants of papillary carcinoma; however, other variants do have clinical implications. **Papillary microcarcinoma** is defined as a papillary carcinoma that measures 1 cm or less in maximum dimension.\(^{11}\) This variant is very common; in some autopsy series it is reported in up to 35.6% of patients, and in surgical series it is found in up to 24% of total thyroidectomies.\(^{11}\) The architectural morphology may be classic, follicular, or oncocytic; the variant may be infiltrative or encapsulated. Microcarcinomas are frequently multiple and, when associated with clinically larger and significant papillary carcinomas, they have been considered to represent dissemination of the larger tumor. However, the evidence points to multifocal primary lesions, as shown by diversity of RET/PTC rearrangements\(^{12}\) and variable X chromosome inactivation.\(^{13}\) Most experts believe that this lesion, when identified incidentally or as an isolated ultrasound abnormality, is of minimal clinical significance;\(^{11}\) it has been suggested that they be called *papillary microtumor* to stay the surgeon’s hand and prevent aggressive management.\(^{14}\) However, this terminology is not widely accepted. Rarely, these lesions can present with metastatic disease\(^{15,16}\); differences between these rare aggressive microcarcinomas and the usual incidental findings have been described with respect to immunoreactivity for cyclin D1 and p27.\(^{15,16}\)

The **solid variant** is considered to comprise approximately 3% of PTCs. This variant characterized by unencapsulated, invasive borders. The cells are arranged in sheets of cells intervened by fibrous stroma. There are vague papillary formations and the follicular pattern is partly maintained. The nuclear morphology is typical of papillary carcinoma. This variant is associated with aggressive behavior and high frequency of distant metastasis, in comparison with a matched group of the classic variant.\(^{17}\)

The **tall cell variant** is an uncommon and infiltrative tumor, considered in some series to represent approximately 10.4% of all papillary carcinomas.\(^{18,19}\) It is composed predominantly of cells whose length is at least 3 times their width (Figure 6). The cells usually have abundant eosinophilic cytoplasm and nuclear morphology that is typical of papillary carcinoma. This variant has a significantly higher incidence of extrathyroidal disease, recurrence, and metastases when compared with a matched group of the usual variant of papillary carcinoma from patients of similar age, sex, and date of diagnosis.\(^{19,19}\) An extreme variant of this form is the **columnar cell variant**, which has such stratification of elongated cells that it resembles endometrial carcinoma.

The **cribriform-morular variant** was first reported in 1994 and was noted to be associated with familial adenomatous polyposis syndrome.\(^{20}\) This variant is characterized by lobules of tumor separated by fibrous septa. The tumor lobules have cribriform architecture characterized by rigid spaces in the lobules formed by arches of cells with no fibrovascular cores (Figure 7). Spindles cells and squamous morules also can be identified. The pathogenesis of these lesions remains an enigma because they harbor ret/PTC rearrangements that are characteristic of regular papillary carcinoma but show no allelic loss of the intact APC gene, as would be expected in tumors associated with familial polyposis coli.\(^{21}\) There is a report of a somatic APC gene mutation rather than a germline mutation in one example of this tumor.\(^{22}\) Although it is rare, the pathologist should be aware of this variant and raise the possibility of underlying APC germline mutations in patients with these variants of PTC.

**PITFALLS IN THE DIAGNOSIS**

There are certain situations that require caution in evaluating nuclear morphology because of morphologic changes that resemble papillary carcinoma.

Reactive changes following fine-needle aspiration were first described by LiVolsi and Merino,\(^{23}\) who used the acronym WHAFFT for worrisome histologic alterations following fine-needle aspiration of thyroid. This WHAFFT condition is characterized by nuclear enlargement, chromatin clearing, and micromucleoli that are similar to nuclei of papillary carcinoma. Vascular changes and capsule pseudoinvasion can be seen. However, the distinguishing features are that these findings are located close to a needle tract and associated with hemorrhage, hemosiderin deposition, linear fibrosis, and capsular dehiscence.

In severe chronic lymphocytic thyroiditis, reactive atypia attributed to inflammation results in nuclear morphology similar to that of papillary carcinoma with nuclear enlargement, chromatin clearing, and even grooves.\(^{7}\) The threshold for nuclear morphology in such cases should be high, and the diagnosis of malignancy should be considered only when there is a discrete nodule with unequivocal architectural changes.

**ANCILLARY STUDIES**

**Immunohistochemistry**

Papillary carcinomas are usually easy to diagnose based on the criteria of nuclear morphology within a nodule. However, there are nodules that have subtle nuclear features, and in the absence of invasive behavior, as in well-circumscribed nodules with follicular architecture, the distinction is difficult,\(^{6}\) but critical, because the differential diagnosis is benign or malignant. In contrast, clearly invasive lesions would be classified follicular or papillary carcinoma, a distinction that is purely academic because the therapy would be the same.

Ancillary tests can help to reach an accurate diagnosis. Several immunohistochemical markers are of some value.\(^{24,25}\) Their application to cytology has also been suggested,\(^{25}\) but there are limitations, as evidenced by the lack of specificity of several markers discussed.

**HBME-1** is a monoclonal antibody that was initially promoted as a marker of mesothelial cells; it is directed against an unknown epitope. In the thyroid, HBME-1 is almost exclusively expressed in malignant neoplasms, including papillary carcinoma, whereas benign lesions are negative. HBME-1 is the most specific marker of thyroid malignancy, but it may not be very sensitive because oncocytic lesions are generally negative; also, many malignancies are not stained by this antibody. HBME-1 positivity is characterized by predominantly membranous staining with variable cytoplasmic staining (Figure 8, a).

**Cytokeratin 19** is a high-molecular-weight cytokeratin that is a sensitive but not specific marker of papillary carcinoma (Figure 8, b). The sensitivity is highest in classic variant lesions and therefore it may not be helpful where it is most needed, in follicular and oncocytic lesions with nuclear atypia. This marker is also strongly expressed in compressed normal thyroid tissue around lesions, in chronic lymphocytic thyroiditis, and in reactive areas of benign tumors, usually around the site of previous biopsy;
Insular Thyroid Carcinoma in Adolescents

A Potentially Lethal Endocrine Malignancy

Ahmed A. K. Hassoun, M.D., Ian D. Hay, M.D., John R. Goellner, M.D., Donald Zimmerman, M.D.

BACKGROUND. Insular thyroid carcinoma is intermediate in aggressiveness between well differentiated and anaplastic thyroid carcinomas.

METHODS. The authors describe two children with insular thyroid carcinoma who had markedly different outcomes. In the first case, a girl age 15 years, 2 months presented with a large pulsatile mass in the right thyroid lobe. In the second case, a girl age 16 years, 3 months presented after total thyroidectomy was performed elsewhere for confirmed pTNM Stage I insular thyroid carcinoma.

RESULTS. In Case 1, total thyroidectomy was performed, and histologic examination revealed insular thyroid carcinoma with lymph node involvement. Six weeks postoperatively, neck masses reappeared. There was significant radioactive iodine uptake in the thyroid bed and in a palpable right supraclavicular lymph node; this was associated with an increased serum thyroglobulin level. Ultrasound-guided biopsy of the lymph node confirmed recurrent insular carcinoma, and neck dissection was performed. Six weeks later, there was 0.35% iodine uptake in the neck, and the patient was treated with 300 mCi of 131I. She had no signs of recurrence when last seen 22 months postoperatively. In Case 2, the patient was given 29.9 mCi of 131I for remnant ablation. Four months postoperatively, fine-needle aspiration biopsy of a high jugular lymph node demonstrated recurrence. The patient was given 200 mCi of 131I but had no significant response. Right modified neck dissection was performed, followed by external beam radiation. Despite aggressive treatment with a further 500 mCi of 131I, progressive lung and mediastinal metastases developed, followed by brain metastasis. The patient died 31 months after the initial diagnosis.

CONCLUSIONS. Insular thyroid carcinoma may occur and behave aggressively in children. Vigorous initial surgical and radioactive iodine treatments are warranted.


KEYWORDS: adolescence, cerebral metastases, insular carcinoma, radioactive iodine, thyroid carcinoma.

Thyroid carcinoma is relatively uncommon in children. The most common type of thyroid malignancy in iodine-sufficient areas in both children and adults is papillary carcinoma. Thyroid carcinoma generally has a better prognosis in children than in adults despite the greater extent of disease at diagnosis in children. Insular thyroid carcinoma, which arises from the follicular epithelium, was initially described in 1984 by Carcangiu et al., who defined its histologic diagnostic criteria. This type of thyroid carcinoma is intermediate in clinical behavior and morphology between well differentiated and undifferentiated (anaplastic) carcinomas. The latest World Health Organization classification includes insular carcinoma among variants of follicular thyroid carcinoma. Recently, it was classified as a separate entity among other thyroid tumors. A few articles have described
In Case 2, distant recurrence also developed, and the patient died as a consequence of metastatic disease in the lung and brain. Tumors from both patients demonstrated a DNA diploid pattern on flow cytometry, as have most of the studied insular carcinomas; this finding reemphasizes that DNA aneuploidy is not necessarily present in aggressive thyroid carcinoma.11

The authors conclude that insular thyroid carcinoma may occur in children. It may cause cancer-related death, as it does in adults, even when it presents with a DNA diploid pattern. Because of the aggressive nature of the tumor, the authors believe that initial management, at any age, should include at least near-total thyroidectomy with appropriate lymph node dissection, followed by remnant ablation and radiiodine therapy for iodophilic metastases.

REFERENCES


ESTABLISHMENT OF A NON-TUMORIGENIC PAPILLARY THYROID CELL LINE (FB-2) CARRYING THE RET/PTC1 REARRANGEMENT

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A novel human thyroid papillary carcinoma cell line (FB-2) has been established and characterized. FB-2 cells harbor the RET/PTC1 chimeric oncogene in which the RET kinase domain is fused to the H4 gene. FB-2 cells neither formed colonies in semisolid media nor induced tumors after hetero-transplant into severe combined immunodeficient mice. However, a number of patients develop recurrences (local or nodal) and distant metastases, or die.3

Tumors of follicular thyroid cells are highly heterogeneous in terms of histology and response to treatment. Malignant thyroid tumors include (i) well-differentiated carcinomas, which comprise follicular (FTC) and papillary (PTC) carcinomas; (ii) poorly differentiated carcinomas; and (iii) undifferentiated carcinomas.1

Well-differentiated PTC is the most frequent type of thyroid cancer and it accounts for the vast majority of thyroid carcinomas associated with previous exposure to ionizing radiation.2 The prognosis of papillary thyroid carcinoma is generally favorable. However, a number of patients develop recurrences (local or nodal) and distant metastases, or die.3

Rearrangements of the RET proto-oncogene represent the most frequent genetic lesion found in thyroid papillary carcinomas.4 These rearrangements cause the fusion of the tyrosine kinase encoding domain of the RET gene to heterologous genes and lead to the generation of the chimeric RET/PTC oncogenes. Several RET/PTC oncogenes have been identified that differ in the fusion partner.5-11 RET/PTC1 and RET/PTC3 are the most prevalent RET/PTC variants.11 In RET/PTC1 and RET/PTC 3, the fusion occurs with the H4 (or D10S170) gene4 and the RFG gene, respectively.7 A chromosomal inversion [inv (10) (q11.2q21)] accounts for the generation of RET/PTC1, whereas a cytogenetically undetectable paracentric inversion within 10q11.2 accounts for RET/PTC 3 activation.11 All the genes fused to RET are ubiquitously expressed and therefore able to drive the expression of truncated forms of RET in thyroid follicular cells that normally do not express it. The RET fusion partners encode dimerization-motif-containing proteins, which mediate constitutive activation of the rearranged RET kinase, phosphorylation of RET on tyrosine residues and chronic stimulation of RET signal transduction.12

RET/PTC oncogenes play a pivotal role in the pathogenesis of human thyroid papillary carcinomas. Indeed they transform thyroid cells in culture,13 and transgenic mice carrying the RET/PTC1 and RET/PTC3 oncogene, under the transcriptional control of the thyroid-specific rat thyroglobulin (TG) promoter, develop thyroid papillary carcinomas.14-16

Cultured cells and cell lines are useful tools with which to study the molecular events leading to neoplastic transformation. Cell lines originating from well-differentiated17-20 or from undifferentiated thyroid carcinomas18,21 have been established. However, few of them have been characterized in terms of biology and molecular aspects.

We describe a new human thyroid cancer cell line, designated FB-2, that was derived from a well-differentiated papillary carcinoma. The FB-2 cell line has been maintained in culture for over 3 years. These cells express several markers of cell transformation but maintain expression of the PAX-8 gene, an important thyroid differentiation marker. Lastly, the FB-2 line carries the RET/PTC1 rearrangement associated with loss of the H4 gene.

MATERIAL AND METHODS

Patient

A thyroid cancer was surgically resected from a 36-year-old woman at the Department of Surgery, S. Chiara Hospital, University of Pisa. A tumor measuring 2 cm was present in the left lobe. There were no neoplastic foci in the remainder of the left lobe or in the right lobe. Neoplastic tissue was cut under sterile conditions. One part was maintained in culture medium, while other parts were frozen in liquid nitrogen and fixed in formalin for histopathology. The tumor had a papillary architecture, and features typical of PTC were identified in the cell nuclei. The tumor was classified “T2N0M0”.

Abbreviations: FBS, fetal bovine serum; PBS, phosphate-buffered saline; PCR, polymerase chain reaction; PDC, poorly differentiated carcinoma; PTC, papillary thyroid carcinoma; RT, reverse transcriptase; TFC, thyroid follicular cell; UC, undifferentiated carcinoma.

Grant sponsor: Italian Association for Cancer Research (AIRC), Milan, Italy.

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Received 18 January 2001; Revised 27 July 2001; Accepted 26 August 2001


**Cell culture**

The neoplastic tissue was finely minced into 1–3 mm pieces. Tissue fragments were washed several times with M-199 medium supplemented with penicillin (500 U/mL), streptomycin (500 U/mL) and nystatin (1,000 U/mL). Tumor tissue was suspended in DMEM medium supplemented with 10% FCS (GIBCO-BRL, Gaithersburg, MD) and incubated at 37°C in a 5% CO₂ atmosphere. The culture medium was changed twice a week. When the culture reached confluence, cells were detached and transferred to new flasks. TCP-1, ARO, FB-1, FB-2 and NPA cells were cultured as described by Cerutti et al. Normal human thyroid cells were obtained and cultured as described by De Nigris et al. 22

**RNA extraction and Northern blot**

We used the guanidine thiocyanate method slightly modified to isolate RNA from cultured cells at passage 30. Northern blots were performed according to standard procedures. 23 The TG, TSH-R, TPO, PAX-8, c-myc, HMGI-C and HMGI(Y)-specific complementary DNA (cDNA) probes used in these experiments are reported elsewhere. 24–26 The random oligonucleotide labeling kit (Amersham, Arlington Heights, IL) was used for probe labeling. 28S and 18S ribosomal RNA were used as molecular-weight markers. GAPDH served to verify uniform RNA loading.

**Assay of transformed phenotype**

Colony-formation in soft agar was performed as previously described. 21 For colonization assay, 500 mL of liquid Matrigel (10 mg/mL) were placed in 16 mm wells of 24-well plates and polymerized at 37°C for 30 min; 5 × 10⁵ cells in complete DMEM were seeded in each well on the top of the gel and incubated at 37°C with 5% CO₂. Cultures were examined 21 days and 10 days after plating, respectively; colonies <60 mm diameter were counted and photographed. For the tumorigenicity assay, 2 × 10⁶ cells were reseeded in 0.2 mL Matrigel and injected subcutaneously into the flanks of immunodeficient female SCID mice (IFFA-Credo, Milan, Italy). The animals were maintained in laminar flow cabinets and given sterile food and acidic water ad libitum. The sites of injection were inspected weekly.

**Chemotaxis and chemoinvasion assays**

The chemotaxis assay was run in Boyden chambers. PVP-free 12 mm polycarbonate filters (Nucleopore, Concord, Italy) were coated with type-IV collagen (5 mg/filter), dried under a hood and reconstituted with DMEM 0.1% BSA before use. Conditioned medium (supernatant of BALB/c 3T3 murine fibroblasts incubated for 24 hr in SFM) was used as chemoattractant in the lower compartment. SFM, containing 0.2% BSA, was the negative control. Cell monolayers were trypsinized, washed and resuspended in SFM; 1 × 10⁵ cells in 0.5 mL were placed in the upper compartment of each chamber. After 6 hr of incubation at 37°C, the cells on the upper surface on the filters were mechanically removed and the filters were fixed and stained. Cells in 8–10 random microscopic fields were counted with a 10× objective; assays were performed in triplicate. The chemoinvasion assay was performed as the chemotaxis assay, except that the polycarbonate filters were coated with liquid Matrigel (12.5 mg/filter) instead of collagen. The Matrigel was dried under a hood and reconstituted with SFM before use. The number of penetrated cells was counted as described above. The number of invading cells/number of chemoattracted cells equals the invasive index.

**Measurement of cytokine levels and IL-6 responsiveness**

Conditioned media from FB-2 cells and other thyroid cell lines were used to measure the release of IL-6, IL-8, IL-10, IL-12, TGFα and TGFβ with immunoenzyme assays. 27 Dosage kits were from R&D Systems, Minneapolis, MN (IL-6, sensitivity 5 pg/mL; IL-8, sensitivity 30 pg/mL; IL-10, sensitivity 10 pg/mL and IL-12, sensitivity 10 pg/mL) and Genzyme, Boston, MA (TGFβ, sensitivity 5 pg/mL; TGF, sensitivity 30 pg/mL). FB-2-conditioned media were withdrawn at 3, 12 and 24 days after plating. TCP-1, ARO and FB-1 cells were used as controls. Responsiveness to IL-6 was analyzed under serum-free conditions as reported elsewhere 28 using recombinant human IL-6 (Genzyme). DNA synthesis was measured as incorporation of [125I]-IUDR (Amersham) 4 days after stimulation with IL-6 (10 and 100 ng/mL) as reported elsewhere. 28

**Analysis of RET/PTC activation**

(i) Genomic DNA extraction and Southern blot analysis were performed according to standard procedures. 25 The DNA samples were digested with EcoRI A 1.0 kb BglII-BamHI fragment specific for the RET proto-oncogene was used as a probe. 26 (ii) The analysis of RET protein expression was performed as previously described. 27 (iii) Polyclonal antibodies against RET were used at 0.1 mg/mL for Western blot and 1 mg/mL for immunoprecipitation. 28 Lysates containing equal amounts of total cellular proteins (500 mg) were subjected to immunoprecipitation with anti-RET antibodies; the immunoprecipitates were subjected to electrophoretic separation and the blots were stained with anti-RET or anti-phosphotyrosine antibodies (pTyr). The 4G10 anti-pTyr monoclonal antibody was purchased from Upstate Biotechnology (Lake Placid, NY).

**RT-PCR analysis**

Reverse transcription and PCR amplification was performed as reported elsewhere. 29 H4 gene expression was analyzed by RT-PCR by using the following primers: H4-forward: 5′-TGCA-GAGGAGAAAAGACCTGTGCT-3′ and H4-reverse: 5′-TTCCTCTGAGCCCTCAAGTCTCCTCTC-3′. The products were analyzed on a 2% agarose gel and hybridized with a RET probe covering the tyrosine-kinase domain. The human hypoxanthine phosphoribosyl-transferase gene was amplified to monitor RNA quality.

**Karyotype analysis**

Cell cultures, at passages 30 and 40, were processed for cytogenetic analysis using standard methods (scolemid exposure, 0.4 mg/mL for 3 hr; hypotonic KCl 0.56% solution for 30 min; methanol-glacial acetic acid 3:1 for 30 min) with quinacrine mustard staining for FQF banding. Consistent results were obtained at the 2 passages. Chromosomes were classified according to international nomenclature. 24 Chromosomal changes were defined “clonal” if present in at least 3 metaphases.

**Fluorescence in situ hybridization (FISH) analysis**

The probes used for dual color FISH analysis were P1 clones RMC10P013, corresponding to the RET gene, and 29F6, corresponding to the H4/D10S170 gene. The order of these probes on 10q is reported elsewhere. 30 The RET probe was labeled with SpectrumGreen™-dUTP and the H4 probe with SpectrumRed™-dUTP (Vysis, Inc., Richmond, UK) using the Nick Translation Kit (Vysis, Inc.). A standard hybridization method was used according to the manufacturer’s protocol. Chromosomes were counterstained with DAPI II (Vysis, Inc.). Twenty metaphase spreads were scored for conventional epifluorescence microscopy and confocal microscopy with digital image capture. In addition, an alpha centromeric probe specific for chromosome 10 (CEP-10, Vysis, Inc.) was used for FISH analysis.

**RESULTS**

**Morphological features of the tumor**

Histologically, the tumor was characterized by a typical papillary architecture (Fig. 1a). The neoplasia invaded the surrounding thyroid tissue but (did not invade the thyroid capsule). Papillary structures were lined by neoplastic cells that had the nuclear features typical of these structures (i.e., elongation, overlapping and grooves). Neither lymph node metastases nor distant metastases were detected. At present (over 4 years after diagnosis), the patient is alive without signs of recurrence. No previous irradiation was reported.
Insular-type component follicular thyroid carcinoma in a 10-year-old girl—case report

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Abstract

Insular-type carcinoma of the thyroid is a rare form of undifferentiated thyroid cancer. The manifestation of disease occurs mainly in adults and is extremely rare in children. Prognosis of this type of thyroid carcinoma is unfavorable in childhood. Because of its rarity, it is not yet clear whether these tumors carry the same risk of progression. Therapy of choice is total thyroidectomy combined with a cervical lymph node dissection. In children, surgery is associated with a higher risk of recurrent nerve palsy and loss of parathyroid glands than in adults. Therefore, identification and protection of the recurrent laryngeal nerve using electrical neuromonitoring as well as exact preparation of parathyroid glands may reduce these risks. The history of a 10-year-old girl with insular-type thyroid carcinoma is presented. Surgical considerations such as total thyroidectomy vs less-than-total thyroidectomy with unilateral or bilateral cervical lymph node dissection are presented. Prognosis concerning morbidity, pointing out the aspect of electrical neuromonitoring and precaution of parathyroid glands, and survival rate of this extremely rare entity are discussed.

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Thyroid carcinoma in childhood was first described in 1902 [1]. Until the 1930s, few cases of such malignomas are presented in the literature [2]. Between the 1930s and the 1950s, an increase in tumor incidence was observed, based on neck irradiation in patients with adenoid or thymus hyperplasia [3]. In the 1960s, after stopping this form of therapy, incidence of thyroid carcinoma decreased, reaching the present incidence of 3 to 5 cases per 100,000 children per year [4]. The Chernobyl power plant accident in 1986 lead to an enormous regional increase of pediatric thyroid carcinomas in Belarus and Ukraine [5].

Generally, etiology of these tumors is unknown. Both familiar genetic disorders and endemic goiter areas and influence of neck radiation and nuclide exposition are discussed in the literature for the development of thyroid carcinoma in children [2].

Thyroid malignomas in childhood are frequently differentiated cancers growing local invasive and lead to distant metastases [2,5]. Histology reveals mostly differentiated carcinomas of papillary type. Extremely rare cases are insular-type carcinomas that show a growth pattern resembling medullary thyroid cancer [6]. Thyroid cancer with insular-type components has a worse prognosis in adults [7]. Prognosis of these tumors in childhood is unknown [8,9]. A case of insular component papillary thyroid cancer in a
10-year-old girl is presented and therapeutic options and prognosis are discussed.

**1. Case report**

At the age of 7 years, our patient complained of painful enlarged lymph nodes on the right side of the neck. At the beginning, a real reason for this affection could not be found. Primarily, it was interpreted as a reactive process to a premolar pulpitis treated by antibiotics. These therapies only lead to a certain reduction of the lymph node swelling. Although palpable lymph nodes persisted, no further investigation was done. Three years later, these nodes enlarged again, and to confirm diagnosis, one lymph node was extirpated. Surprisingly, histology revealed lymph node metastasis of papillary thyroid carcinoma. At that stage, the girl was referred to our Department of Pediatric Surgery. The predisposing cause of her disease was unknown. Neither thyroid carcinoma in family case history nor radiation exposition of the neck was preloaded. Examination showed hard but painless lymph nodes on the right side of the neck (up to 3 cm in diameter) and a solid resistant tumor at the right upper pole of the thyroid gland (about 2-5 cm in diameter). Ultrasonography and technetium 99m 2-methoxyisobutylisonitrile scan (Tc MIBI scan) suggested characteristics of malignant tumor. Computed tomography without contrast revealed no associated tumor occurring with multiple endocrine neoplasia syndrome. Immunohistology of the lymph node specimen showed thyreoglobulin-positive reaction. Serum calcitonin was within normal range.

Surgical therapy consisted of a right-sided functional neck dissection including the central and the right lateral lymph node compartments and total thyroidectomy. The right upper pole of the thyroid gland showed a hard tumor with macroscopic, undoubtedly malignant tissue infiltrating the strap muscles as well as the right cricothyroid muscle. Total thyroidectomy under precaution of all 4 parathyroid glands could be performed, especially on the left thyroid lobe; two parathyroid glands were identified and their vascular supply was protected. For identifying the recurrent laryngeal nerve (RLN), neuromonitoring (Neurosign 100, Magstim Company, UK) with a needle probe placed into the vocal cord muscle by penetrating the cricothyroid membrane was used. Then, the vagus nerve was identified in the vascular sheet and stimulated with a probe using 1 mA. When a clear acoustic signal was reached, the whole loop of the recurrent nerve was ensured to be intact (Fig. 1). All laryngeal nerves could be found but the right external branch of the superior laryngeal nerve was involved within the tumor and had to be sacrificed.

Lymph node dissection on the left compartment was not performed because no clinical and no radiologic/scintigraphic signs of lymph node metastases could be confirmed. Within the first days after operation, the girl had slight hypocalcemia, which had to be treated with calcium for 2 weeks. Postoperative laryngoscopy showed intact vocal cord function.

**Final histological examination** was follicular variant of papillary carcinoma with infiltration of the adjacent muscles. Inside the tumor, components of insular growth and concomitant vascular invasion could be found (Fig. 2). Immunohistochemistry with p53-specific antibodies showed no staining of carcinoma.

Further postoperative recovery was uneventful. Six weeks after total thyroidectomy, 80-mCi radiiodine treatment under hypothyroid condition was carried out. After 6 months, MIBI scan showed a circumscribed activity in the right lower central neck compartment. Radioiodine therapy had to be repeated with 150 mCi and 3 months later with 100 mCi. After 4 years, thyreoglobulin level is within a normal range (<4 ng/mL) and ultrasound shows no sign of tumor recurrence.

![Fig. 1 Stimulation of the left RLN by the neuromonitoring probe (arrow) and left upper and lower parathyroid glands (asterisks).](image1.png)

![Fig. 2 Insular-type carcinoma invasion into a blood vessel. The histological growth pattern resembles medullary thyroid carcinoma.](image2.png)
2. Discussion

Insular carcinoma of the thyroid was first described as “Wuchernde Struma” by Langhans [10] in 1907. This histology pattern was not regarded as a special tumor entity until 1984 when Carcangiu et al [6] described this disease systematically. Insular thyroid carcinoma, which is characterized by islets of solid cell clusters resembling medullary thyroid cancer, occurs predominantly in adults older than 50 years. Concerning prognosis quoad vitam, insular carcinoma is graded between well-differentiated papillary/follicular carcinoma and anaplastic carcinoma [4]. Components of insular thyroid carcinomas within areas of differentiated carcinomas confirm the theory of dedifferentiation. In childhood, differentiated form of thyroid carcinoma is very rare with an actual incidence of 3 to 5 cases per 1,000,000 children per year [2,12]. Therefore, differentiated thyroid carcinoma combined with insular-type components is considered as an extremely rare entity. Our patient had follicular type of a papillary thyroid cancer including vessel invading insular carcinoma components. Consequently to this rarity, only poor knowledge about prognosis of this tumor type exists [11]. In adults, Sasaki et al [7] show a worse prognosis in differentiated carcinomas of the thyroid gland with insular components. Among 44 adults, 17 patients died of the disease, 2 are alive with progression of disease, and 18 are alive disease free. The 5-, 10-, and 20-year survival rates of this series are 80%, 66%, and 40%, respectively [7].

Zettinig et al [8] reported a case of differentiated thyroid carcinoma with insular-type components in a 14-year-old girl. This patient had lung metastases at diagnosis and was treated with total thyroidectomy and unilateral functional neck dissection and repeatedly radioiodine therapy (postoperative, 80 mCi; 4 months later, 200 mCi; and 1 year postoperative, 150 mCi). This patient was disease free 24 years after diagnosis and gave birth to two healthy children [8].

Dedifferentiated thyroid carcinoma in childhood is associated with a higher rate of local infiltrative growth and higher incidence of mainly lung metastases than in adults [2]. Our patient had local cervical infiltrative growth and conglomerates of multiple lymph node metastases without distant metastases.

Therapeutic modality in carcinomas of thyreocyte origin in children is total thyroidectomy combined with unilateral or bilateral functional neck dissection and radioiodine therapy [2-4]. However, morbidity of total thyroidectomy in children is relatively high [1-3]. Rates of recurrent nerve palsy up to 24% and rates of permanent hypoparathyroidism up to 27% are reported [4]. In our patient, neuromonitoring with the Neurosign 100 (Magstim Company) was very useful to identify and protect the recurrent nerves. In our patient, the ramus externus of the superior laryngeal nerve could be identified on both sides but had to be sacrificed on the right side because of tumor infiltration. Tumor infiltration of the RLN occurs in more than 30% of cases, which may be the reason for the high rate of nerve palsies, which is twice the rate of adults [8]. Generally, thyroid malignancies in children are diagnosed at an advanced tumor stage, which may be the result of delayed diagnosis and possibly the reason for higher dedifferentiated tumor activity. Probably, our patient had delay of 3 years until diagnosis was confirmed by lymph node biopsy. The possibility to develop another primary malignancy in a child treated for thyroid cancer is higher than in adults, either caused by radioiodine therapy or as a result of a yet unknown genetic defect (Thompson G, personal communication, June 2004).

3. Conclusion

In childhood, total thyroidectomy is the best management option in all cases of thyreocyte-derived carcinoma based on the high rate of multicentricity of papillary thyroid carcinoma and possible dedifferentiation of residual tumor cells into undifferentiated thyroid carcinoma. Furthermore, total thyroidectomy makes radioiodine therapy much more effective, as well as thyreoglobulin can be used as a tumor marker. One important argument against total thyroidectomy in children is the experience that recurrent nerve palsies and hypoparathyroidism had a double higher risk compared with adults. Therefore, it is recommended that thyroidectomy and functional neck dissection in children should be performed by an experienced and specialized surgeon. In addition, neuromonitoring may be helpful to identify and protect recurrent and superior laryngeal nerves [12].

References

2. Discussion

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Differentiated thyroid carcinoma in childhood is associated with a higher rate of local infiltrative growth and higher incidence of mainly lung metastases than in adults [2]. Our patient had local cervical infiltrative growth and conglomerates of multiple lymph node metastases without distant metastases.

Therapeutic modality in carcinomas of thyreocyte origin in children is total thyroidectomy combined with unilateral or bilateral functional neck dissection and radioiodine therapy [2-4]. However, morbidity of total thyroidectomy in children is relatively high [1-3]. Rates of recurrent nerve palsy up to 24% and rates of permanent hypoparathyroidism up to 27% are reported [4]. In our patient, neuromonitoring with the Neurosign 100 (Magstim Company) was very useful to identify and protect the recurrent nerves. In our patient, the ramus externus of the superior laryngeal nerve could be identified on both sides but had to be sacrificed on the right side because of tumor infiltration. Tumor infiltration of the RLN occurs in more than 30% of cases, which may be the reason for the high rate of nerve palsy, which is twice the rate of adults [8]. Generally, thyroid malignancies in children are diagnosed at an advanced tumor stage, which may be the result of delayed diagnosis and possibly the reason for higher dedifferentiated tumor activity. Probably, our patient had delay of 3 years until diagnosis was confirmed by lymph node biopsy. The possibility to develop another primary malignancy in a child treated for thyroid cancer is higher than in adults, either caused by radiiodine therapy or as a result of a yet unknown genetic defect (Thompson G, personal communication, June 2004).

3. Conclusion

In childhood, total thyroidectomy is the best management option in all cases of thyreocyte-derived carcinoma based on the high rate of multicentricity of papillary thyroid carcinoma and possible dedifferentiation of residual tumor cells into undifferentiated thyroid carcinoma. Furthermore, total thyroidectomy makes radioiodine therapy much more effective, as well as thyreoglobulin can be used as a tumor marker. One important argument against total thyroidectomy in children is the experience that recurrent nerve palsy’s and hypoparathyroidism had a double higher risk compared with adults. Therefore, it is recommended that thyroidectomy and functional neck dissection in children should be performed by an experienced and specialized surgeon. In addition, neuromonitoring may be helpful to identify and protect recurrent and superior laryngeal nerves [12].

References

2. Discussion

Insular carcinoma of the thyroid was first described as “Ueber die epithelialen Formen der malignen Struma” by Langhans [10] in 1907. This histology pattern was not regarded as a special tumor entity until 1984 when Carcangiu et al [6] described this disease systematically. Insular thyroid carcinoma, which is characterized by islets of solid cell clusters resembling medullary thyroid cancer, occurs predominantly in adults older than 50 years. Concerning prognosis quoad vitam, insular carcinoma is graded between well-differentiated papillary/follicular carcinoma and anaplastic carcinoma [4]. Components of insular thyroid carcinomas within areas of differentiated carcinomas confirm the theory of dedifferentiation. In childhood, differentiated form of thyroid carcinoma is very rare with an actual incidence of 3 to 5 cases per 1,000,000 children per year [2,12]. Therefore, differentiated thyroid carcinoma combined with insular-type components is considered as an extremely rare entity. Our patient had follicular type of a papillary thyroid cancer including vessel invading insular carcinoma components. Consequently to this rarity, only poor knowledge about prognosis of this tumor type exists [11]. In adults, Sasaki et al [7] show a worse prognosis in differentiated carcinomas of the thyroid gland with insular components. Among 44 adults, 17 patients died of the disease, 2 were alive with progression of disease, and 18 were alive disease free. The 5-, 10-, and 20-year survival rates of this series are 80%, 66%, and 40%, respectively [7].

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Treatment of sporadic nonmedullary thyroid carcinomas in pediatric age

Paola Collini, Franco Mattavelli, Claudio Spinelli and Maura Massimino†

Nonmedullary thyroid carcinomas are rare malignancies in pediatric ages. The vast majority of them are papillary carcinomas with an overall survival of approximately 100%. Their outcome is independent of strong prognostic factors of adults, such as papillary carcinoma histological subtype, invasion into soft tissue of the neck, presence and site of distant metastases, relapse and type of surgery. In these ages, follicular carcinomas and poorly differentiated carcinomas are exceptional. Undifferentiated (anaplastic) carcinomas are practically absent. In most institutions, the therapy of choice for all pediatric thyroid carcinomas is the radical approach, aimed at the eradication at diagnosis of all clinical and subclinical neoplastic foci, both at thyroid, lymph node and distant level. It consists of total thyroidectomy and lymphadenectomy in children with clinically evident lymph-node metastases, followed by radioactive iodine therapy independent of histotype and stage. Recently, owing also to the high sensitivity to hormonal manipulation shown by pediatric papillary carcinomas, a conservative approach has been proposed for selected cases, consisting of the removal of only the grossly detectable disease followed by thyroid-stimulating hormone-suppressive hormonal therapy to control subclinical disease. Today, the existence of two therapeutic approaches, radical versus conservative therapy, should be considered whenever treating a child or adolescent with a nonmedullary thyroid carcinoma. Not least, permanent post-treatment complications of radical surgery and radioactive iodine therapy should be taken into account. The future tasks include the stratification of thyroid carcinomas into low- and high-risk cases, also including their molecular alterations and the possibility of a molecularly targeted therapy against tyrosine kinases involved in the pathogenesis of thyroid carcinomas.

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Diagnostic Utility of Intracytoplasmic Lumen and Transgressing Vessels in Evaluation of Hürthle Cell Lesions by Fine-Needle Aspiration

Yi J. Yang, MD, PhD; Kamal K. Khurana, MD

Hürthle cells are thyroid follicular cells with abundant granular cytoplasm. Hürthle cell nodules of the thyroid can result from nonneoplastic conditions such as Hashimoto’s thyroiditis, adenomatous goiter, and Graves’ disease. Conversely, neoplastic nodules may be composed of Hürthle cells. Although Hürthle cells can be readily identified by their unique cytomorphology in thyroid fine-needle aspirates (FNAs), the cytogentic distinction of Hürthle cell neoplasms (HCNs) from nonneoplastic lesions with prominent Hürthle cells may be difficult. Hürthle cell atypia associated with Hashimoto’s thyroiditis can lead to a false diagnosis of HCN. Accurate diagnosis of HCN has relied on virtually exclusive presence of Hürthle cells and their collection in aspirate smears.

This approach is objective but relatively insensitive, because isolated collection of Hürthle cells may also represent Hürthle cell nodules resulting from nonneoplastic conditions. Hürthle cell neoplasms associated with Hashimoto’s thyroiditis may be missed in aspiration cytology if the neoplastic cells are overlooked and if the diagnosis is based on the cells arising from thyroiditis.

Recent reports and abstracts have emphasized the importance of intracytoplasmic lumen (ICL) and transgressing vessels (TV) as useful criteria enabling distinction of neoplastic from nonneoplastic Hürthle cell lesions in thyroid aspirates. The purpose of this retrospective study was to evaluate if these suggested criteria (TV and ICL) resulted in any improvement in the sensitivity and specificity of the cytogentic diagnosis of HCN when compared with the conventional criteria used for diagnosis of neoplastic Hürthle cell lesions in our laboratory.

MATERIALS AND METHODS

The cytopathology files at the University Hospital of SUNY Upstate Medical University, Syracuse, NY, dated between January 1993 and December 1998 were reviewed for cytologic diagnosis of HCN, nonneoplastic thyroid with prominent Hürthle cell component, and Hashimoto’s thyroiditis. Only those cases with adequate smears and available follow-up histopathologic diagnosis were included in this study. According to the guidelines of the Papanicolaou Society of Cytopathology, examination of FNA of thyroid nodules was considered adequate if there were at least 5 groups of well-preserved, well-visualized follicular cells with each group containing 10 or more cells. All of the FNA specimens were stained by both Papanicolaou and Diff-Quik methods. Hematoxylin and eosin was used routinely for surgical pathology slides (sections fixed in formaldehyde solution and embedded in paraffin).
In our laboratory, cytologic diagnosis of a HCN is made based on the conventional criteria as described by Kini et al. These criteria include cellular aspirates showing a predominance of a relatively monotonous population of Hürthle cells (75%), singly or in dyshesive aggregates associated with little or no colloid, the absence of lymphocytic infiltrate, and a scarcity of ordinary follicular cells. Our lab diagnosis of nonneoplastic thyroid lesion (including Hashimoto’s thyroiditis and goiter) is based on the presence of follicular centers and interlobular fibrosis. The follicular epithelium frequently exhibited Hürthle cell change. In nodular goiter individual cells, follicles or groups of follicles with Hürthle cell cytology may be encountered. Briefly, histologic diagnosis of Hürthle cell neoplasm required an identification of an isolated mass in the thyroid composed exclusively of Hürthle cells and found in a gland not affected by chronic thyroiditis. Identification of transcapsular invasion, vascular invasion, or destructive invasion of the capsule resulted in diagnosis of Hürthle cell carcinoma. Hashimoto’s thyroiditis was characterized by accentuation of lobulation of normal gland by prominent lymphoid and plasma-cell infiltrate with the presence of follicular centers and interlobular fibrosis. The follicular epithelium frequently exhibited Hürthle cell change. In nodular goiter individual cells, follicles or groups of follicles with Hürthle cell cytology may be encountered. The majority of the nonneoplastic Hürthle cell nodules composed entirely of Hürthle cells represent Hürthle cell change of preexisting follicular adenomatous nodules in goiters and thyroiditis. In general, nonneoplastic Hürthle cell nodules lack encapsulation, may exhibit multicentricity and macrofollicular growth pattern, and occur in a background of nodular goiter or Hashimoto’s thyroiditis.

Sensitivity, specificity, positive predictive value, negative predictive value, and test efficiency were determined using the standard definitions: sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); positive predictive value = TP/(TP + FP); negative predictive value = TN/(TN + FN); test efficiency = (TP + TN)/(TP + TN + FP + FN), in which TP = true positive, TN = true negative, FP = false positive, and FN = false negative. To determine the true or false status, the FNA diagnoses were classified by each of the authors for the purpose of rendering cytologic diagnoses. If 1 or both of these features were identified, a cytologic diagnosis of HCN was rendered. Absence of these features resulted in diagnosis of nonneoplastic thyroid. The percentage of concordant cytologic diagnoses between 2 pathologists (K.K. and Y.Y.) was also determined.

Histologic findings in cases of Hürthle cell adenoma, Hürthle cell carcinoma, and Hashimoto’s thyroiditis have been described previously. Briefly, histologic diagnosis of Hürthle cell neoplasm required an identification of an isolated mass in the thyroid composed exclusively of Hürthle cells and found in a gland not affected by chronic thyroiditis. Identification of transcapsular invasion, vascular invasion, or destructive invasion of the capsule resulted in diagnosis of Hürthle cell carcinoma. Hashimoto’s thyroiditis was characterized by accentuation of lobulation of normal gland by prominent lymphoid and plasma-cell infiltrate with the presence of follicular centers and interlobular fibrosis. The follicular epithelium frequently exhibited Hürthle cell change. In nodular goiter individual cells, follicles or groups of follicles with Hürthle cell cytology may be encountered. The majority of the nonneoplastic Hürthle cell nodules composed entirely of Hürthle cells represent Hürthle cell change of preexisting follicular adenomatous nodules in goiters and thyroiditis.

### RESULTS

A total of 30 FNAs with histologic follow-up were identified. The patient population consisted of 27 women and 3 men ranging in age from 22 years to 76 years, with a mean age of 46 years. Based on the conventional criteria used in our laboratory, an original cytologic diagnosis of HCN was rendered in 13 cases, and diagnosis of nonneoplastic thyroid (including Hashimoto’s thyroiditis and goiter with Hürthle cell metaplasia) was rendered in 17 cases. Table 1 shows the follow-up histopathologic diagnosis in all cases with cytologic diagnosis of HCN and 20 cases of nonneoplastic thyroid lesions (including Hashimoto’s thyroiditis and goiter). Table 2 shows the reclassified cytologic diagnoses of nonneoplastic and neoplastic thyroid based on the presence or absence of TV and/or ICL. Reclassified cytologic diagnoses as rendered by each pathologist (Y.Y. and K.K.) were concordant in 100% of cases. Transgressing vessels were usually prominent and readily identified in both Diff-Quik and Papanicolaou stains (Figure 1). Intracytoplasmic lumens, however, were only seen in Diff-Quik-stained smears (Figure 2).

### Table 1. Fine-Needle Aspirate (FNA) Diagnoses Using Conventional Criteria and Follow-up Histopathologic Diagnoses

<table>
<thead>
<tr>
<th>FNA Diagnosis (n)</th>
<th>Surgical Follow-up (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hürthle cell neoplasm (13)</td>
<td>Hürthle cell adenoma (6)</td>
</tr>
<tr>
<td>Hürthle cell carcinoma (3)</td>
<td>Hashimoto’s thyroiditis (4)</td>
</tr>
<tr>
<td>Nonneoplastic thyroid (17)</td>
<td>Hürthle cell carcinoma (1)</td>
</tr>
<tr>
<td></td>
<td>Hashimoto’s thyroiditis (12)</td>
</tr>
<tr>
<td></td>
<td>Nodular goiter (4)</td>
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</tbody>
</table>

### Table 2. Reclassification of Fine-Needle Aspirate Diagnoses After Application of New Criteria*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Hürthle Cell Neoplasm Cases</th>
<th>Nonneoplastic Hürthle Cell Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICL</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>TV</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>ICL and TV</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>ICL or TV</td>
<td>13</td>
<td>17</td>
</tr>
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* ICL indicates intracytoplasmic lumen; TV, transgressing vessels.
Follicular Thyroid Lesions Coexisting With Hashimoto’s Thyroiditis: Incidence and Possible Sources of Diagnostic Errors

Our objectives were to study the types and incidence of thyroid follicular lesions coexisting with Hashimoto’s thyroiditis (HT), the pitfalls in their cytodiagnosis, and the effect on management. All cases of HT diagnosed by fine-needle aspiration (FNA) and/or histology over a 7-yr period were retrospectively studied. HT coexisted with follicular adenoma (FA) in 6 cases, follicular variant of papillary carcinoma (FVPC) in 1 case, and goitrous nodule (GN) in 2 cases. The overall incidence rates of thyroid neoplasm and goitrous nodules coexistent with HT were 15% and 3.5%, respectively. A preoperative FNA diagnosis was available in 10 histologically proven cases of HT. A false-positive diagnosis of follicular neoplasm (FN) that led to unnecessary thyroidectomies was given in 3 cases. In 2 of these, the cytological diagnosis was HT with the possibility of coexisting FN, and in the third case, the cytological finding of HT was misinterpreted as FN. The main causes of these diagnostic pitfalls were the presence of hyperplastic follicular cells with nuclear pleomorphism, a paucity of lymphoid cells in burned-out HT, and lack of ones exposure. Nuclear pleomorphism was observed in none of the follicular adenomas. FNA diagnosed accurately the coexisting lesions in 6 cases; 3 FA, 1 FVPC, and 2 GN, but it did not sample HT. In one case, FNA diagnosed correctly both HT and the coexisting FA. Therefore, the presence of a coexistent neoplasm or goitrous nodule reduced the chances of sampling HT by 85.7%, with no false-negative results. Indeed, aspiration on and around the thyroid nodule helps in sampling HT. However, HT may dominate the smear and obscure neoplasia. This can be avoided if the procedure is performed by the pathologist and the aspiration is done on the nodule only. The overlapping cytological features of FN and HT were the main causes of false-positive results. This can be reduced by avoiding the diagnosis of FN in the presence of follicular-cell pleomorphism and/or moderate to excessive numbers of lymphoid cells, provided proper aspiration technique is maintained. Diagn. Cytopathol. 2003;28:35–38. © 2002 Wiley-Liss, Inc.

Key Words: Hashimoto’s thyroiditis; follicular thyroid lesions; cytodiagnosis

Hashimoto’s thyroiditis (HT) is an autoimmune disease of the thyroid gland commonly encountered in females of middle age. The diagnosis is primarily clinical and serological. The main aim of thyroid fine-needle aspiration (FNA) is to assist in the diagnosis of neoplastic diseases. However, the technique is accurate and acceptable in the diagnosis of HT, especially antibody-negative cases. HT is known to coexist with neoplastic and nonneoplastic diseases of the thyroid gland. The cytological features of HT overlap with some of these lesions, especially follicular neoplasm (FN), leading to both false-negative and false-positive results, which may have a negative impact on management. In this study, the incidence and various types of thyroid lesions associated with HT are presented. The sources of pitfalls in their cytodiagnosis were also analyzed, with the emphasis on their effect on management.

Materials and Methods

All FNA and histopathology reports of HT diagnosed between October 1994–May 2002 were retrieved from the files of the Histo/Cytopathology Section in the Central Laboratories, PARAS Central Hospital (Al-Jouf, Saudi Arabia). A retrospective review of these FNA and thyroidectomy cases formed the basis of this study. FNA was performed by the pathologist, using 23-gauge needles. In cases of a solitary nodule, only the lesion was aspirated, and the surrounding glandular tissue was avoided. The air-dried
Hürthle cells encountered in HT is very difficult. Reported incidence rates of coexisting thyroid neoplasia with HT ranged between 3–14%.\textsuperscript{1,3,4,6} In our study, the overall incidence rate was 15%. In the present study, lesions coexistent with HT were mainly of follicular type. The associated lesion alone was sampled and diagnosed in 6 cases, among which 3 were FA, 1 was FVPA, and 2 were GN. The presence of well-defined palpable thyroid nodules reduced the chances of sampling HT by 85.7%. However, this has no implication in management, which would be surgical whether HT is diagnosed or not. It is true that HT was missed in these cases, but in contrast to others,\textsuperscript{3,6,7} false-negative results were not reported during the review period. This could be due to differences in the size of lesions sampled, as in our cases, the lesions were rather sizable, ranging between 1.5–3.0 cm. Another possible cause was the sampling technique employed. In our study, all lesions were aspirated by the pathologist. In the presence of well-defined thyroid nodules, only two passes were made on the nodule proper, while the surrounding glandular area was avoided as much as possible. The whole gland was only aspirated in cases of bilateral diffuse or nodular enlargement. In common practice, FNA is performed by surgeons or radiologists, and the aspiration is done on and around the nodule.\textsuperscript{1,7} We presume that our technique of sampling the nodule and avoiding the surrounding glandular tissue was quite appropriate, and because of this technique we did not miss any cases of FN coexisting with HT. Aspirating the neighboring glandular tissue may help in diagnosing HT, but the cytological features of HT may dominate the smears and overshadow the coexisting neoplasm with false-negative results.

False-positive results led to unnecessary thyroidectomies in 3 of our cases. In 2 of these, the possibility of follicular neoplasia could not be excluded, and in the third, the cytological features of HT were misinterpreted as FN. In the first 2 cases, the smears showed hyperplastic follicular epithelial cells outnumbering lymphocytes. These cells were similar to those of follicular adenomas. The three-dimensional arrangement of follicular cells, which is regarded as a feature of neoplastic processes, was also seen in these smears. We observed that nuclear pleomorphism was noted in HT and not in follicular adenomas. The presence of hyperplastic follicular cells in HT is a common cause of error, as has been reported by most workers\textsuperscript{1,4,6,7} who tried to probe the causes of false-positive results. Some authors\textsuperscript{6,7} found that the cytological differentiation between hyperplastic follicular cells of HT and those of follicular neoplasia was too difficult, and one of them advised that the diagnosis of FN should not be given along with HT.\textsuperscript{3} This would eliminate false-positive results, but can be a cause of false-negative ones, as we accurately diagnosed a case of follicular adenoma associated with HT in the present study. Cytological atypia was considered by some workers not to be a useful criterion in differentiating HT from FN.\textsuperscript{4,10} In spite of the fact that our material dealt with a small number of cases, we felt that a follicular-cell pleomorphism was more in favor of HT. The pleomorphism of follicular cells in HT must be of reparative or reactive nature. The proportion of lymphoid cells to follicular cells is important. In the case diagnosed correctly as FN + HT, the lymphoid component was minor and focal, whereas in those cases diagnosed cytologically as HT with the possibility of associated FN, the lymphoid component was moderate to excessive and diffuse. We believe that the diagnosis of FN should be avoided in the presence of moderate or excessive numbers of lymphocytes. In the last case of our series, HT was misinterpreted as FN due to the relative paucity of lymphocytes. Histologically, the case was found to be burned-out HT, with mainly fibrosis and hyperplasia of follicular cells and Askanazy’s cells. After reviewing the smears from this case, it was seen that the misinterpretation of cytological features was due to lack of ones exposure to similar cases. In these smears, the lymphocytes were so sparse that the interpreter could have mistaken them as being of blood origin. The sparse occurrence of giant cells, large reactive lymphocytes, and plasma cells was overlooked. Their identification should have hinted at the correct diagnosis (especially large reactive lymphocytes and plasma cells), as they are not seen in the normal blood picture. To conclude, the diagnosis of FN is unlikely and better to be avoided in the presence of a follicular-cell pleomorphism and/or moderate to excessive numbers of lymphocytes. The aspiration on and around the thyroid nodule helps in sampling HT, but may lead to false-negative results. These can be avoided if the aspiration is done by the pathologist and only on the nodule.

References

Special Variants of Differentiated Thyroid Cancer: Does It Alter the Extent of Surgery Versus Well-Differentiated Thyroid Cancer?

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Abstract

Introduction: Recently, more aggressive variants of so-called well-differentiated thyroid carcinomas have been identified such as the tall cell variant, columnar cell variant, diffuse sclerosing variant, insular carcinoma, and Hürthle cell (oncocytic, oxyphilic) carcinomas.

Methods: An evidence-based review was performed to identify the optimal treatment recommendations for these thyroid cancers of intermediate differentiation.

Conclusions: Although some variation exists within the group, aggressive surgical and medical management are recommended for these neoplasias. Any such recommendations should, however, be viewed in the light of the fact that the current literature mainly consists of case reports, case series, and limited reviews. The clinical presentation, pathophysiology, diagnosis, and surgical and medical management for these thyroid cancers with intermediate differentiation are discussed.

Classically, primary thyroid cancer has been divided into well-differentiated thyroid cancer (WDTC; papillary and follicular thyroid cancer), comprising approximately 90% of the cases, medullary thyroid cancer (MTC; arising from the thyroid C-cells) 5%–9% of the cases, whereas the remaining 1%–2% are anaplastic or poorly differentiated cancers (Table 1).1,2 Within the category of WDTC, however, various histological subtypes have evolved due to an improved understanding of their biology. In contrast to the overall indolent behavior of the classical WDTC, subtypes of these tumors have been identified as being more aggressive and thus have been labeled thyroid cancers with intermediate differentiation. These include variants of papillary thyroid cancer such as the tall cell variant (TCV), columnar cell variant (CCV), diffuse sclerosing variant (DSV), as well as insular carcinoma (IC), and Hürthle cell (oncocytic, oxyphilic) carcinomas (HCC; Table 1).3,4 Typically, MTC is also classified as intermediate differentiated and is discussed elsewhere in this issue of World Journal of Surgery.

Even though the intermediate variants of thyroid cancer comprise only 10%–15% of all thyroid cancers, knowledge of their unique features, natural history, and management are essential as they typically differ from those of WDTC. The current literature mainly comprises case reports and small series and accordingly, management guidelines must be viewed in this light. The level of scientific evidence upon which recommendations are made tends to be level IV or V (Table 2). The clinical presentation, pathophysiology, diagnosis, and management of TCV, CCV, DSV, IC, and HCC in contrast to WDTC are reviewed, with a focus on surgical management.
Special Variants of Differentiated Thyroid Cancer: Does It Alter the Extent of Surgery Versus Well-Differentiated Thyroid Cancer?

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Abstract

Introduction: Recently, more aggressive variants of so-called well-differentiated thyroid carcinomas have been identified such as the tall cell variant, columnar cell variant, diffuse sclerosing variant, insular carcinoma, and Hürthle cell (oncocytic, oxyphilic) carcinomas.

Methods: An evidence-based review was performed to identify the optimal treatment recommendations for these thyroid cancers of intermediate differentiation.

Conclusions: Although some variation exists within the group, aggressive surgical and medical management are recommended for these neoplasias. Any such recommendations should, however, be viewed in the light of the fact that the current literature mainly consists of case reports, case series, and limited reviews. The clinical presentation, pathophysiology, diagnosis, and surgical and medical management for these thyroid cancers with intermediate differentiation are discussed.

Classically, primary thyroid cancer has been divided into well-differentiated thyroid cancer (WDTC; papillary and follicular thyroid cancer), comprising approximately 90% of the cases, medullary thyroid cancer (MTC; arising from the thyroid C-cells) 5%–9% of the cases, whereas the remaining 1%–2% are anaplastic or poorly differentiated cancers (Table 1).1,2 Within the category of WDTC, however, various histological subtypes have evolved due to an improved understanding of their biology. In contrast to the overall indolent behavior of the classical WDTC, subtypes of these tumors have been identified as being more aggressive and thus have been labeled thyroid cancers with intermediate differentiation. These include variants of papillary thyroid cancer such as the tall cell variant (TCV), columnar cell variant (CCV), diffuse sclerosing variant (DSV), as well as insular carcinoma (IC), and Hürthle cell (oncocytic, oxyphilic) carcinomas (HCC; Table 1).3,4 Typically, MTC is also classified as intermediately differentiated and is discussed elsewhere in this issue of World Journal of Surgery.

Even though the intermediate variants of thyroid cancer comprise only 10%–15% of all thyroid cancers, knowledge of their unique features, natural history, and management are essential as they typically differ from those of WDTC. The current literature mainly comprises case reports and small series and accordingly, management guidelines must be viewed in this light. The level of scientific evidence upon which recommendations are made tends to be level IV or V (Table 2). The clinical presentation, pathophysiology, diagnosis, and management of TCV, CCV, DSV, IC, and HCC in contrast to WDTC are reviewed, with a focus on surgical management.
Special Variants of Differentiated Thyroid Cancer: Does It Alter the Extent of Surgery Versus Well-Differentiated Thyroid Cancer?

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Overall, extrathyroidal extension of the tumor at diagnosis was found in 40%, and cervical adenopathy in 68% of the cases. During a mean follow-up period of 8.2 years, average rates of locoregional recurrence, distant metastasis, and tumor-related mortality were 13%, 19%, and 2% respectively. Based on the current evidence, DSPTC appears to have the same favorable long-term prognosis as the usual PTC; however, larger number of patients and longer follow-up would be necessary to clarify this issue. The management of DSPTC should begin with awareness on the part of the treating physician of the ability of this tumor to mimic thyroiditis at presentation. Given the propensity for this tumor to infiltrate intrathyroidal lymphatics and the high rate of nodal metastases a total thyroidectomy with an en bloc resection of locally infiltrating structures combined with a modified neck dissection for regional lymphadenopathy is advised. The high propensity for lymph node involvement suggests that adjuvant radioiodine therapy should be considered in all cases of DSPTC.

**INSULAR THYROID CARCINOMA**

Carcangiu et al. established diagnostic criteria for a distinctive type of thyroid cancer with solid clusters of cells or “insulae” and a propensity to metastasize to regional lymph nodes and distant sites. However, Langhans had already in 1907 described a tumor with small uniform neoplastic cells in a characteristic nesting pattern. Over 200 cases of insular thyroid cancer have been described in the literature. Insular thyroid cancer is a tumor of intermediate differentiation and biological aggressiveness, accounting for between 2% and 6% of all thyroid cancers. Similar to WDTC, IC occurs more commonly in females, with a female-to-male ratio of greater than 2:1, and the age at presentation is typically in the mid-50s. The tumors of IC are significantly larger than those of WDTC with a mean diameter greater than 5 cm.

On cytology, IC tumors show high cellularity, scant colloid, and no psammoma bodies (Fig. 6). The cellular pattern is that of well-formed nests of cells in combination with many single cells. The cells are mostly round to oval in shape. The nuclear to cytoplasmic ratio is high and nuclear overlapping is a prominent feature. The microscopic features as described by Carcangi are the guidelines used by most pathologists. The important features are formation of solid clusters of tumor cells containing a variable number of small follicles; small size and uniformity of tumor cells; a variable but consistently present mitotic activity; capsular and blood vessel invasion; and frequent necrotic foci (Fig. 7). The IC appears to be an aggressive subtype of thyroid cancer that has been shown in a number of case series to have a high propensity for local recurrence, distant metastasis, and increased mortality. In a review of more than 200 cases, extrathyroidal extension of the tumor at diagnosis was found in 44%, and cervical adenopathy in 51%. During a mean follow-up period of 72 months, average rates of locoregional recurrence and/or distant metastasis, and tumor-related mortality were 64% and 32% respectively.

The rarity of this tumor makes it difficult to draw conclusions from the literature as to the best treatment op-
tion. In order to utilize radioactive iodine postoperatively and ensure complete tumor extirpation, a total thyroidectomy should be performed whether the insular component is more than 50% of the tumor volume or not. With over 50% of IC having regional nodal metastases, central node dissection should be performed in all cases and a modified radical neck dissection should be considered. In view of the high rate of regional and distant metastases, adjuvant radioiodine treatment should be considered in all cases, though prospective evidence for its use is not available. The role of external radiotherapy has not been clarified; however, patients with unresectable disease, incompletely excised tumors, and loco-regional recurrences may benefit from external beam radiation.

HU¨RTHELLE CELL (OXYPHILIC; ONCOCYTIC) CARCINOMAS

These belong to the subgroup of follicular thyroid carcinoma (FTC), which represent 5% or fewer cases of well-differentiated thyroid cancers in countries with iodine-sufficient diets. HCC metastasize to lung, lymph nodes, bone, and brain in about 30% of the cases, in contrast to corresponding figures of 15%–20% in usual FTC.

Hürtle cell neoplasms are encapsulated collections of Hürtle cells, large polygonal eosinophilic cells with pleomorphic hyperchromatic nuclei and fine granular acidophilic cytoplasm (Fig. 8). Since Hürtle cells are commonly associated with Hashimoto’s thyroiditis, and Graves’ disease, multiple needle passages are required to reliably diagnose Hürtle cell neoplasms. Similar to FTC, fine needle aspiration cannot distinguish between benign and malignant Hürtle cell neoplasms, and 20%–25% will prove to be malignant.

Patients with follicular and Hürtle cell neoplasms should undergo operative exploration, and the minimal operation is a thorough neck exploration, an ipsilateral thyroid lobectomy and isthmectomy, and palpation of the contralateral gland. This is adequate treatment for a benign Hürtle cell tumor. However, if the lesion proves to be a carcinoma most experts agree that total thyroidectomy is the treatment of choice. As previously mentioned, the only way to distinguish between malignant and benign disease is by the presence of vascular and/or capsular invasion, which can rarely be determined either pre- or intraoperatively (Fig. 9). However, at exploration, if evidence of malignancy, such as invasion of adjacent structures or lymph node metastasis, is present, the authors confirm malignancy by obtaining a guided frozen section, and if malignant, perform an initial total thyroidectomy. We would also perform an initial total thyroidectomy for a Hürtle cell neoplasm if the patient had a history of head and neck irradiation or if bilateral macroscopic nodular thyroid disease is present. HCC tends to have a more aggressive clinical course, as evidenced by a higher incidence of metastasis, decreased propensity for 131I uptake, and lower survival rates. Carcangi et al. have shown that local recurrence of HCC is correlated with the extent of surgery, with recurrence rates for nodelectomy, thyroid lobectomy, and total thyroidectomy of 75%, 40%, and 15% respectively. Additionally, 65% of Hürtle cell neoplasms larger than 4 cm will prove to be malignant. Thus, we recommend performing total thy-
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 "suspicous 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 "suspicous" 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.

Key Words: Thyroid Gland; Thyroid Nodule; Biopsy, Fine-Needle; Child; Adolescent

INTRODUCTION

Thyroid nodules are uncommon in children and adolescents compared with adults, but the risk of malignancy is much higher (14 to 40% in children compared with 5% in adults) (1-5). In adults, fine needle aspiration biopsy (FNAB) has been used extensively for the management of thyroid disease and for patient selection for surgical exploration with a high degree of reliability (4, 5). However, FNAB has not been utilized extensively for the evaluation of thyroid nodules in the young; and relevant data in the literature are often in disagreement (2, 6-10). To assess the utility of FNAB for the management of children and adolescents, we reviewed our experience with FNAB for thyroid nodules in children and adolescents.

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 (11).

RESULTS

Fifty-one children and adolescents underwent FNAB, and a total of 60 FNABs were performed on these patients. Pa-
patients’ ages ranged from 2 to 21 yr with a mean age of 17 yr. Sixteen (27%) of the patients were 2 to 13 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 “benign”. The cytological diagnosis in three cases was Hashimoto’s thyroiditis. Five (8%) of the aspirates were diagnosed as “suspicious 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 “suspicious 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 “suspicious” 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 atrophic follicular epithelial cells and a few scattered macrophages in the bloody background (Fig. 2).

Table 1. Cytological diagnoses by fine needle aspiration biopsy

<table>
<thead>
<tr>
<th>Diagnostic category</th>
<th>Age group</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-15 yr old (%)</td>
<td>16-21 yr old (%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>2 (13%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Suspicious</td>
<td>1 (6%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Benign</td>
<td>13 (81%)</td>
<td>32 (73%)</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>0 (0%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>44</td>
</tr>
</tbody>
</table>

DISCUSSION

In adults, FNAB has become a part of the routine evaluation of thyroid nodules. Since its introduction, the percentage of patients that undergo thyroidectomy has decreased by 25% to 50% with the use of FNAB (6). But FNAB has been underutilized for the evaluation of thyroid nodules in the young because of the possibility of complications and the need for sedation. In our practice, sedation is rarely required and no complications have arisen. In our opinion, FNAB is a relatively simple procedure with few complications.

Internal and external reports of predominantly adult patients with thyroid nodules show that the sensitivity of thyroid FNAB ranges from 80-100% with a specificity of 90-100% (3-5, 12-15). Investigations of FNAB in pediatric thyroid nodules have shown a wide range of sensitivities (7-10). Degnan et al. (7) reported on 18 children who underwent surgery after thyroid FNAB and found a sensitivity of 50%. Similarly, Lugo-Vicente et al. (8) reported on 24 children who underwent thyroidectomy for thyroid nodules, and a retrospective review of the cytological materials of 18 cases that received preoperative thyroid FNAB revealed a sensitivity of 60%. Thus, because of its apparent low sensitivity, they concluded that FNAB did not have a primary role in surgeon’s decision regarding the surgical management of these patients. However, Corrias et al. (9) reported on 42 children who underwent surgery after thyroid FNAB and found a sensitivity of 95%. Moreover, Amrikachi et al. (10) reported a sensitivity of 100% in 218 child and adolescent thyroid aspirates. In the present study, we also achieved a sensitivity of 100%. These better results are similar to those obtained in adults and suggest that FNAB is highly effective at selecting patients for surgery without missing malignant lesions.

The reported specificities of thyroid FNAB in pediatric thyroid nodules ranges from 65 to 90% (7-10). In our study, its specificity of 65% was lower than usual. The one cause of low specificity might be associated with statistical problem. Amrikachi et al. (10) suggested that because most cases with a negative FNAB result were followed up clinically, it was difficult to estimate the true negative diagnosis in the follow-

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

<table>
<thead>
<tr>
<th>Cytological diagnosis</th>
<th>Histological diagnoses</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Suspicious for</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>papillary carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular neoplasm</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Benign</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
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 oncocytes, 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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