CASE REPORT

Thyroid nodule with Hashimoto thyroiditis in childhood – a challenging experience

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Abstract
Fine-needle aspiration biopsy (FNAB) of the thyroid, although not perfect, is considered currently the best preoperative method in establishing malignancy in a thyroid nodule. We report the case of an 8-year-old girl with a thyroid mass in the right thyroid lobe. Endocrine investigations revealed subclinical hypothyroidism and high titer of anti-thyroid peroxidase antibodies. Fine Needle Aspiration Biopsy (FNAB) of the right side of the thyroid gland, where on thyroid ultrasonography (US) a poorly defined iso-/hypoechoic nodule with irregular margins was detected, revealed a background of lymphocytes and plasma cells mixed with follicular cells with reactive changes. After four months of treatment with L-thyroxine, ultrasonographic follow up showed an increase in nodule size. FNAB was performed again but showed non-diagnostic cytology. Right lobectomy was performed and the pathology report shows papillary carcinoma, follicular variant predominantly with components of insular growth. We discuss the false-negative FNAB interpretation because of the concomitant autoimmune thyroiditis. Management strategy for this case and the prognosis is also discussed.

Keywords: autoimmune thyroiditis, insular variant, papillary carcinoma.

Introduction
In childhood and adolescence thyroid nodules are an uncommon finding, their prevalence ranges between 0.2–1.44 % and are 5–10 times lower than in adults [1]. However, any nodule discovered in this age group should be viewed with suspicion and the diagnostic approach should be more aggressive in children than in adults because they are more often malignant than in adults. The mean incidence of thyroid carcinomas in childhood thyroid nodules that were operated on shows an overall malignancy risk of 26.4% [2].

We report in this article the presentation of a young girl with a rapidly enlarging thyroid mass, despite our medical treatment. A discussion of the case and review of the existing experience of this disease in children follows.

Patient, Methods and Results
An 8-year-old girl of Caucasian origin was referred to our Department for evaluation of a thyroid mass. She had presented two weeks earlier to her primary physician with a palpable mass in the right thyroid lobe. She denied sore throat, had a normal appetite and no bowel symptoms. No history of radiation exposure or family history of thyroid malignancy was identified.

Her growth, weight and height were on the 25th percentile for age. Pubertal status was Tanner I (B1, PH1), blood pressure 80/60, and pulse regular (92 beats per minute). Neck examination revealed a non-tender, firm and mobile enlarged right lobe of the thyroid. No cervical lymphadenopathy was noted. The remainder of her examination was unremarkable.

Thyroid ultrasonography (US) revealed increased thyroid volume (4.5 mL), with diffuse hypoechogenicity and pseudomultinodular aspects in the right lobe. A poorly defined iso-/hypoechic nodule measuring 1.3/0.9 cm with irregular margins was detected in the right lobe. The left lobe and isthmus had no nodules.

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Endocrine investigations at this moment revealed:
- TSH = 8.91 mIU/L (normal ranges 0.22–4.2 mIU/L);  
- FT4 = 0.98 ng/mL (normal ranges 0.9–1.9 ng/mL);  
- T3 in the normal range;  
- Anti-thyroid peroxidase antibodies, ATPO = 634 IU/mL (normal ranges ≤34 IU/mL);  
- Serum calcitonin level was normal.

Fine Needle Aspiration Biopsy (FNAB) of the right side of the thyroid gland revealed numerous lymphoid cells at different stages of maturation and follicular epithelial cells, some of them hyperplastic, in acinar clusters with vesicular nuclei and scant cytoplasm. The follicular cells nuclei were slightly pleomorphic but no well-formed intranuclear cytoplasmatic inclusions or nuclear grooves were reported (Figure 1).

All this changes were interpreted as reactive with the recommendation of a close clinical follow up.

Treatment with 25 µg thyroxine once daily was started. Ultrasonographic follow up 5–6 weeks later showed the same multinodular images in the right thyroid lobe but a slightly decreased total thyroid volume. At this time, TSH was 4.17 mIU/mL.
After another two months US examination showed an increase in nodule size (2.5/1.4 cm) with a complex pattern, irregular margins, and enhanced internal color flow by Doppler. In addition, a cervical lymph node, 1.2 cm in diameter was identified. FNAB was performed again but showed non-diagnostic cytology. We decided to perform right lobectomy.

Pathology report

One fragment of thyroid tissue consisting of right thyroid lobe, measuring 4×3×2 cm, was sent for examination. The fragment had a smooth surface and a multinodulated, white appearance on section. Histological sections of the tumor showed a neoplasm composed of polyhedral cells with formation of small, deformed follicles. There are vague papillary formations and the follicular pattern is partly maintained (Figure 2).

Nuclear morphology of the follicular cells was characterized by the following constellation of features: enlarged and elongated nuclei with crowding and overlap, nuclear grooves, irregular nuclear contour with fine chromatin, reminiscent of those seen in papillary carcinoma (“orphan Annie eyes”). Micronucleoli located immediately underneath the nuclear membrane and intranuclear cytoplasmic pseudoinclusions were also described. Inside the tumor, areas of neoplastic cells organized into insular, cord-like, and sheet-like arrangements have been described, with rare areas presenting hyper eosinophilia of colloid. Frequently, the insular arrangements contained microfollicular structures. In general, the microfollicles did not contain colloid. Although there was no typical necrosis the insular architecture was very constant and characteristic (Figure 3).

Peritumoral intense desmoplastic reaction and vascular emboli were present. The neoplasm did not invade the thyroid capsule. The surrounding thyroid tissue displayed a few small lymphoid follicles with germinal centers and small aggregates of benign lymphoid cells, in keeping with autoimmune thyroiditis (AT).

Pathology conclusion was papillary carcinoma, follicular variant predominantly with components of insular growth and concomitant vascular emboli. Total thyroidectomy with paratracheal and cervical lymph node resection has been proposed. Radioiodine ablation will be undertaken.
Discussion

Carcinomas of the thyroid gland are rare pediatric tumors, representing up to 1.5–3% of childhood and adolescence malignancies. As in adults among carcinomas derived from the follicular epithelium papillary thyroid carcinoma is the most frequent histotype, constituting about 90% of pediatric cases, whereas follicular and poorly differentiated carcinomas are exceptional. The actual incidence of differentiated form of thyroid carcinoma in childhood is estimated to 3–5 cases per 1,000,000 children per year [2].

Within the category of so-called well-differentiated thyroid carcinomas (papillary and follicular thyroid carcinoma) more aggressive variants have been identified such as the tall cell variant, diffuse sclerosing variant, columnar cell variant, insular carcinoma or Hürthle cell (oncocytic, oxyphilic) carcinomas. These subtypes, because of their clinical behavior, have been labeled thyroid cancers with intermediate differentiation [3].

Langhans first described insular carcinoma of the thyroid as “Wuchernde Struma”, in 1907. But only in 1984 Carcangiu ML et al. [4] described systematically the histology pattern as a special tumor entity. Insular thyroid carcinoma, which is characterized by islets of solid cell clusters, occurs predominantly in adults older than 50 years, more commonly in females, with a female-to-male ratio greater than 2 : 1. Components of insular thyroid carcinomas within areas of well-differentiated carcinomas confirm the theory of dedifferentiation.

The insular phenotype does not have yet the exact genetic and molecular events elucidated. A point mutations, CAA->AAA transversion, at codon 61 of the N-RAS gene have been described in three insular carcinoma cases [5]. Transversion mutations are more common in poorly differentiated carcinomas of the thyroid compared with transition mutations. Mutations of the RAS gene are also associated with distant metastases in follicular, poorly differentiated, and undifferentiated thyroid neoplasms [6]. Other candidate genes responsible for the insular phenotype include p53, Bcl2 and cyclin D1 [7]. An increased immunohistochemical staining for basic fibroblast growth factor was evident.

One of the most controversial aspects in our case concerns prognosis. Our patient had follicular variant of a papillary thyroid carcinoma with insular component, considered an extremely rare entity. Consequent to this rarity, only poor knowledge about prognosis of this tumor type in children exists.

A case of differentiated thyroid carcinoma with insular-type components in a 14-year-old girl who had lung metastases at diagnosis has been reported. This patient, after total thyroidectomy and unilateral functional neck dissection and repeatedly radiiodine therapy, was disease free 24 years after diagnosis and gave birth to two healthy children [8]. In contrast, Hassoun AA et al. [9] report two cases of insular carcinoma in two adolescent girls with early evidence of lymph node metastasis, in one of this distant recurrence also developed, and the patient died as a consequence of metastatic disease in the lung and brain. It is very difficult to draw a conclusion regarding prognosis in this specific type of thyroid carcinoma in children, a review of the literature done by Yusuf K et al. [6] suggested a relatively high mortality of 18%. In adults, a number of case series of insular carcinoma showed that this tumor has 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 loco-regional recurrence and/or distant metastasis, and tumor-related mortality were 64% and 32% respectively [3].

In our case, we made the recommendations for completion thyroidectomy. This is the current recommendation whether the insular component is more than 50% of the tumor volume or not, even in children where morbidity of this procedure is considered relatively high. Rates of recurrent nerve palsy up to 24% and of permanent hypoparathyroidism up to 27% has been reported [10]. Appropriate lymph node dissection should be associated and adjuvant radiiodine ablation is generally employed in pediatric thyroid cancer, though prospective evidence for its use is not available and not all-insular carcinoma take up 131I. The ablative dose of 131I in children is 1 mCi/kg body weight. The roles of chemotherapy and external radiation therapy in this type of cancer remain to be defined [11].

Another aspect need to be mentioned is the coexistence of autoimmune thyroiditis (AT) in our case. From our knowledge, this is the first case described in the literature of these associations in childhood [6, 8, 9, 12–14].

Autoimmune thyroiditis (AT) is a chronic disorder with an occurrence prevalence of 1.3% to 9.6% in childhood and adolescence [15]. The prevalence of thyroid cancer among patients with AT is still a matter of controversy. Many investigators looked for an association between autoimmune thyroiditis and thyroid cancer, some of the studies [16, 17] reported a prevalence range from 1% to 30%. This high variability is associated with geographic and ethnic diversity in the prevalence of AT and thyroid cancer which had led to differences in patient selection. The observation of a more favorable course of thyroid cancer in the presence of AT raised the supposition that lymphocytic infiltration may represent an immune reaction to control proliferation of cancerous cells. In this context AT has also been described as a protective factor. This hypothesis has not been supported by more recent evidence [2].

Many of these data refer almost exclusively to adults. A very new study [18] analyzes the relationship between AT, cancer, and thyroid nodules in a large case series of pediatric patients. Despite the limitation of a retrospective study design, this new data show that thyroid nodular disease is present in 31.5% of pediatric patients with AT and that cancer occurs among these in at least 9.6% of cases, with papillary carcinoma being the most common histological type.
We must emphasize the roll of the iodine status in AT. Our patient came from a region known to be mild to moderate iodine deficient where iodine prophylaxis was made in the last years. There are some data in the literature showing that iodine prophylaxis in a previously iodine-deficient area and its relative excess in the diet should be considered as responsible for both AT and carcinoma [2].

The most important point of discussion is the role of FNAB in management of thyroid nodules in childhood. FNAB is a relatively simple procedure with few complications that has become a part of routine evaluation of thyroid nodules in adults. For many years, FNAB has been underutilized for the evaluation of thyroid nodules in children and adolescents because of the possibility of complications and the need for sedation. Few data are available and there are still many questions without unanimous answer such as is FNAB a safe and accurate procedure for children? Some of the studies suggest that FNAB biopsy of thyroid nodules in young patients has similar high sensitivity and specificity as the procedure in the adult population [2, 19]. However, in others, the accuracy of FNAB is less than reported for adults and a more aggressive diagnostic and therapeutic approach in children and adolescents than for adults is recommended [20].

FNAB is carried out to obtain adequate follicular cells that can be difficult in children especially in highly vascularized tumors where more investigations on the same day could be necessary. In our patient, the first FNAB performed was interpreted with caution because of the concomitant AT in the hypothyroid phase. It is well known that an elevated TSH promotes goiter development and could be responsible for morphological changes in epithelial follicular cells. Some authors found that the cytological differentiation between hyperplasic follicular cells of AT and those of follicular neoplasia was too difficult, and one of them advised that the diagnosis of follicular lesion should not be given along with AT [21, 22]. This would eliminate false-positive results, but can be a cause of false-negative ones, as in our case.

Two clinical features were very important in our decision to refer this girl to the surgeon: first was the presence of the right lymphadenopathy. Thyroid cancer in children is characterized by loco-regional lymphadenopathy in 35–83% of cases, which is much higher than in adults. Based on findings among children with thyroid nodules, with or without AT, the presence of an enlarged lymph node ranks second after FNAB in accurate detection of malignancy [18]. The second feature was the increases in nodule diameter during levothyroxine therapy. Some investigators [18, 23] claim that a lack of reduction in nodule diameter during levothyroxine therapy is prognostic of a malignant nature of the nodule.

### Conclusions

FNAB is a good screening test for thyroid nodules in children but should not be performed if AT coexists, until the patient is euthyroid. However, the additional use of various clinical variables like finding of lymphadenopathy and increase in nodule diameter during therapy can be helpful in choosing the right therapeutically strategy. Insular carcinoma of the thyroid is a very rare form of thyroid cancer in children, does not have the excellent prognosis seen with follicular or papillary carcinoma, and therefore warrants aggressive treatment. Near-total thyroidectomy, appropriate lymph node dissection, and adjuvant radioiodine ablation are generally employed.

### References

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