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Autonomous functioning thyroid nodule in a child: Management dilemmas

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Abstract:

Autonomous functioning thyroid nodules (AFTNs) are characterized by hyperfunctioning nodules within an otherwise normal thyroid gland, predominantly affecting adults and rarely observed in pediatric populations, especially pre-pubertal children. The management of AFTNs in children is complex due to their rarity and the potential long-term consequences of treatment. While radioiodine ablation (RAIA) is a common treatment in adults, its application in children is limited by concerns about growth, fertility, and cancer risks. Alternative treatments include conservative management with antithyroid drugs or observation, and surgical options like hemithyroidectomy. This manuscript presents a case report of a nine-year-old girl with AFTN-induced thyrotoxicosis, outlining the diagnostic and therapeutic challenges associated with this condition in children. The case underscores the need for individualized treatment

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strategies in pediatric AFTNs, balancing the benefits and risks of various modalities. The rarity of AFTNs in children, combined with the paucity of standardized guidelines, highlights the necessity for further research to optimize management outcomes in this population.

Keywords: Autonomous functioning thyroid nodule, Hemithyroidectomy, Radioiodine ablation, Anti-thyroid drugs, Thyroid cancer

Introduction

Autonomous functioning thyroid nodules (AFTNs) are characterized by the presence of a hyperfunctioning nodule in an otherwise normal thyroid gland [1]. While AFTNs are commonly seen in adults, they are quite rare in children, especially in the pre-pubertal age group. Management of AFTN in children poses unique challenges due to their rarity and the potential long-term consequences of treatment. While radioiodine ablation (RAIA) is a well-established modality in adults, its use in pediatric patients is limited by concerns regarding its effects on growth, fertility, and the risk of thyroid and other forms of cancer [2]. Conservative management, including pharmacological treatment with antithyroid drugs or observation alone, may be considered as an alternative to RAIA. Additionally, hemithyroidectomy has been proposed as a viable option for treating AFTN in children [3]. Nonetheless, the optimal management strategy for AFTNs in children remains uncertain, necessitating individualized approaches that balance the risks and benefits of various treatment modalities.

In this context, we present a case report of a nine-year-old female child with an AFTN causing thyrotoxicosis, highlighting the diagnostic challenges and management dilemmas encountered with this rare condition in pediatric patients.

Case report

A nine-year-old girl presented to us with complaints of swelling on the right side of her neck. Clinical examination revealed a palpable nodule in the right lobe of the thyroid gland, which was non-tender and moved with deglutition [Fig 1A and B]. There were no signs of inflammation. She complained of weight loss of 2-3 kgs, palpitations, and increased frequency of stools for the past two months. Thyroid function tests revealed elevated serum free tri-iodothyronine (FT3) of 10.47 pg/mL [normal range (N): 2.58-4.02 pg/mL], elevated free thyroxine of 2.29 ng/dL (N:

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0.65-1.06 ng/dL), elevated tri-iodothyronine of 2.41 ng/mL (N: 1.05-2.07 ng/mL) and elevated thyroxine (T4) of 13.7 µg/dL (N:5.01-12.45 µg/dL), and suppressed thyroid stimulating hormone (TSH) <0.01 µIU/mL (N: 0.35-5.50 µIU/mL), all parameters measured by chemiluminescence (CLIA). Ultrasound of the thyroid showed an enlarged right lobe with a solitary isoechoic nodule of size approximately 37 x 24 mm, with regular margins and increased blood flow on colour Doppler, TIRADS score 2. The left lobe of the thyroid was normal in size, echotexture, and blood flow.

Technetium 99 (Tc-99m) pertechnetate thyroid scintigraphy (thyroid scan) revealed a hyperfunctioning hot nodule in the right lobe of the thyroid gland [Fig 2A and B] with a relative uptake of 96.5% and an absolute uptake of 4.9%. There was a suppression of background activity, with an uptake of only 0.2% in the left lobe [Fig 3A and B]. Based on the clinical presentation, thyroid function test results, ultrasound, and thyroid scan findings, the diagnosis of an AFTN was established.

After a comprehensive discussion of the pros and cons of each treatment option, a consensus was reached between the medical team and the patient's parents to initiate antithyroid medication therapy with carbimazole. The family was reluctant for hemithyroidectomy. The decision to start carbimazole at a dose of 10 mg daily was made to mitigate the patient's thyrotoxicosis, alleviating her symptoms, and preserving thyroid function. Regular follow-up appointments were planned to monitor the patient's thyroid function, assess treatment response, and adjust medication dosage as needed.

Furthermore, recognizing the potential need for definitive therapy in the future, it was decided that when the patient reached around 18 years of age, she would be considered for radioiodine ablation (RAIA). This long-term plan aims to provide the patient with a permanent cure for her AFTN while minimizing the risks associated with surgery and radiation exposure during childhood.

Discussion

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AFTNs are relatively rare in pediatric patients compared to adults. The exact prevalence of AFTNs in children is not well-established due to their rarity. However, studies suggest that AFTNs account for a small proportion of thyroid nodules in pediatric populations, ranging from 1% to 5% of all thyroid nodules [4].

Despite their low prevalence, AFTNs can present significant clinical challenges in pediatric patients, including thyrotoxicosis, compressive symptoms, and potential disturbances in growth and puberty due to impaired thyroid function.

The pathogenesis of AFTNs involves genetic, molecular, and environmental factors. Somatic mutations in the TSH receptor gene (TSHR) or G-protein alpha subunit gene (GNAS) have been implicated in the autonomous functioning of thyroid nodules [5]. These mutations lead to constitutive activation of the cyclic adenosine monophosphate (cAMP) pathway, resulting in increased thyroid hormone production and secretion independent of TSH stimulation. Additionally, alterations in intracellular signaling pathways, such as the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway, contribute to the autonomous function of thyroid nodules [5,6]. Environmental factors, such as iodine deficiency or excess, may also influence the development of AFTNs by affecting thyroid hormone synthesis and metabolism [7]. In our patient, due to financial constraints, genetic analysis for somatic mutations could not be done.

The diagnostic workup of AFTNs includes clinical evaluation, thyroid function tests, thyroid imaging, and fine-needle aspiration cytology (FNAC). Clinical examination may reveal a palpable thyroid nodule, which is typically non-tender and moves with swallowing. Thyroid function tests often demonstrate elevated FT3 and FT4 levels, with suppressed TSH levels, consistent with thyrotoxicosis, as was present in our patient. Thyroid imaging modalities, such as technetium 99 thyroid scan or ultrasound, can further characterize the nodule and assess its functional status. FNAC may be performed to rule out malignancy in indeterminate cases, although it is routinely not required [8].

The risk of cancer in AFTNs in children is generally considered to be low, 0-1% [4, 9]. Only one study from western Poland reported a cancer risk of 29% in pediatric AFTN [10]. This might be

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related to a higher prevalence of iodine deficiency and exposure to radiation from the Chernobyl nuclear disaster in that region [4, 10].

While AFTNs are benign in most cases, the possibility of coexisting thyroid cancer cannot be entirely ruled out [8]. Therefore, vigilance is warranted, particularly in cases with atypical features or suspicious findings on diagnostic imaging or fine-needle aspiration cytology.

The management of AFTN in children presents a significant dilemma. The American Thyroid Association (ATA) recommends hemithyroidectomy as the first-line treatment for pediatric AFTNs, taking into account the risks associated with radioiodine ablation (RAIA) and reports indicating that one-third of AFTNs may harbour co-existing thyroid cancer [8]. However, the ATA also suggests that surgery may be deferred in children with mild thyrotoxicosis [8]. Hemithyroidectomy provides definitive therapy by removing the hyperfunctioning thyroid nodule. This approach is particularly suitable for patients with large or symptomatic nodules, those experiencing compressive symptoms, or those who prefer surgical intervention. Despite this, many families may be reluctant to pursue this option due to the associated surgical risks, such as damage to the recurrent laryngeal nerve and hypoparathyroidism. Additionally, the need for lifelong thyroid hormone replacement therapy post-surgery should be considered.

Radioiodine ablation is typically reserved for cases that are resistant to medical therapy or in patients who are not candidates for surgery. While RAIA effectively destroys hyperfunctioning thyroid tissue, it carries the risk of radiation exposure and the potential development of thyroid cancer later in life in pediatric patients. Due to concerns regarding the mutagenic effects of low-activity radioiodine on normal thyroid tissue, the ATA currently does not recommend RAIA for children [8].

Antithyroid medications, such as carbimazole or methimazole, which inhibit thyroid hormone synthesis, are often used as the initial treatment for pediatric AFTNs, particularly in those who do not prefer hemithyroidectomy. These medications effectively control thyrotoxicosis and reduce nodule size in most cases. Nonetheless, long-term compliance and potential side effects, including agranulocytosis, hepatotoxicity, and skin rash, pose challenges.

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Similar to AFTN, the management of Graves' disease in pediatric and adolescent age groups poses significant dilemmas. According to the recently published European Thyroid Association Guidelines on the treatment of Graves' disease in children and adolescents, RAIA use in very young children (under 5 years) is considered a near-absolute contraindication due to the higher long-term theoretical risk of malignancy [11]. For children aged 5 to 10 years, RAIA is seen as a relative contraindication. Notably, the guidelines now recommend that antithyroid drugs (ATDs) should be maintained for multiple years in pediatric patients with Graves' disease [11]. This approach allows children with a near-absolute or relative age-based contraindication for RAIA to remain on ATDs until they reach an age where they can safely undergo RAIA.

Thus, the management of pediatric AFTNs poses several dilemmas, including the selection of the most appropriate treatment modality, consideration of long-term implications and outcomes, and involvement of the patient and their family in decision-making. Treatment decisions should be individualized based on patient age, comorbidities, nodule characteristics, and family preferences. Additionally, close monitoring for potential complications, such as medication side effects, surgical risks, or radiation-related adverse effects, is essential to optimize patient care.

Conclusion

Pediatric AFTNs are rare but require careful management to optimize outcomes. Treatment decisions should be tailored to individual patient needs, considering the pathogenesis, diagnostic workup, treatment options, and long-term implications. Further research is needed to establish standardized guidelines for the management of AFTNs in children and to improve our understanding of the underlying mechanisms driving thyroid nodule autonomy.

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Figure legends

1. A and B - Anterior and lateral images of the neck showing a right-sided thyroid nodule.

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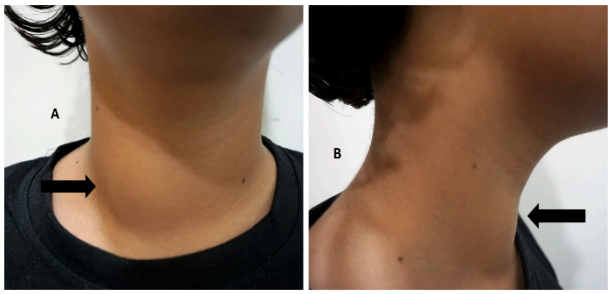
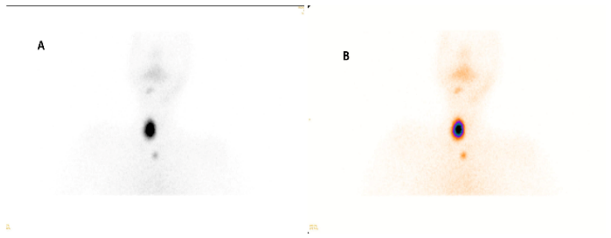
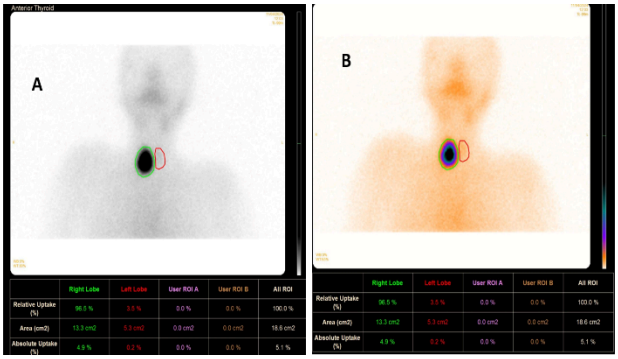


2. A and B - Black and white and coloured images of a Technetium-99m thyroid scan showing a hyperfunctioning nodule in the right lobe.



3. A and B - Black and white and coloured images of a Technetium-99m thyroid scan showing uptake in both the right and left lobes of the thyroid.



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