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Papillary thyroid microcarcinoma in a boy with Graves' disease: a case report and review of the literature

Brodawkowaty mikrorak tarczycy u chłopca z chorobą Gravesa-Basedowa: przypadek i przegląd literatury

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Abstract
A 16-years old boy with diagnosis of Grave's disease was treated with methimazole for one year before radical total thyroidectomy treatment due to persistence of clinical hormonal hyperthyroidism. Histological analysis revealed the presence of a papillary microcarcinoma. The management of Grave's disease in pediatric age is still under discussion. Therefore, close monitoring of the disease is required, as well as case-by-case tailored decision on how to manage treatment and when to perform the radical one, taking into account the association of Grave's disease with differentiated thyroid cancer in adults and the higher malignancy of thyroid cancer in childhood.
Key words:
Grave's disease, thyroid cancer, pediatric age.

Introduction

Hyperthyroidism is defined as a thyrotoxic disorder in which thyroid hormones are synthesized and secreted in excess by the thyroid gland. The disease occurs in about 1 out 5000 children and adolescents, representing about 1–5% of diagnosed cases of hyperthyroidism in all age groups [1]. Hyperthyroidism in pediatric age is mainly linked to Graves' disease, an autoimmune disorder in which stimulation of the TSH-receptor by autoantibodies (TRAb) causes thyroid hyperplasia and dysregulation of thyroid hormones production.

Medical treatment with antithyroid drugs (ATD), such as methimazole at 0.2–0.5 mg/kg/day in 1–3 doses, represents the first-line treatment for Graves' disease in children and is performed with either dose titration (DT) or block and replace (BR) approach. Additional treatment with β-blockers, such as propranolol 1–2 mg/kg in 2–3 doses, is also indicated during the first 2–4 weeks of treatment with ATD, when cardiac symptoms of hyperthyroidism are severe or poorly tolerated [1, 2].

Disease remission after two years of treatment occurs in one third of pediatric cases, compared to 40–60% in adults [1, 2]. a long-term ATD regimen is needed in another third of cases, while the remaining third requires radical treatment, which can be surgical or with radioiodine [1, 2].

In patients with Graves' disease periodic ultrasound follow-up is recommended to rule out nodular thyroid disease. In adult patients with hyperthyroidism, recent studies have shown an increase in the rate of differentiated thyroid cancer (DTC), with an incidence of 4.7–81.1%, especially in the presence of nodules; to date very few data are present for the pediatric age [3–7]. The most represented type of DTC is papillary microcarcinoma and the co-presence of Graves' disease does not appear to be associated with more aggressive tumor behaviour [5, 6].

We present the case of an adolescent with clinical manifestations of hyperthyroidism, difficult to compensate, who underwent total thyroidectomy. Histological analysis of the removed thyroid tissue revealed papillary microcarcinoma.

Case report

A 16-years-old boy with hereditary spherocytosis was referred to our Department as he reported palpitation, restless sleep and asthenia in the last few weeks. Family history was positive for thyroid disease (autoimmune hypothyroidism in the

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maternal lineage, including the mother, and autoimmune hyperthyroidism in the paternal lineage); recent pathological hystory revealed frequent abdominal pain and severe asthenia.

At medical examination, he had visible and palpaple thyroid struma, moderate exophthalmos, and tachycardia. Biochemical investigations confirmed low serum TSH and high serum levels of free thyroid hormones (TSH 0.007 μUI/ml, fT4 39 pg/ml, fT3 15 pg/ml), with positive thyroperoxidase antibodies (AbTPO > 3000 UI/l) and TRAb (13.8 UI/l). The height was 173 cm, the weight 49 kg, the BMI 16.4 kg/m^2 and he presented adult Tanner stage.

Thyroid ultrasound showed an enlarged gland (left lobe 20 × 21 mm; right lobe 21 × 21 mm), with inhomogeneous echostructure, without visible nodules or diffuse hypervascularization.

Based on clinically and biochemically confirmed hyperthyroidism, treatment with methimazole 15 mg/day (0.3 mg/kg/day) was started and propranolol 40 mg/day (0.8 mg/kg/day) was added to control cardiac symptoms.

After one month of therapy, weakness and asthenia were still present, while the palpitation episodes had disappeared. Biochemical investigations revealed an improvement in thyroid metabolism, with TSH 0.040 μUI/ml, fT4 7.5 pg/ml, fT3 3.4 pg/ml, therefore the methimazole dose was reduced to 7.5 mg/day (0.15 mg/kg/day) and β-blockers treatment was discontinued

Six months after treatment with ATD, asthenia and sleep restlessness persisted and it was difficult to achieve normalization of the thyroid hormone profile. After several dose titrations of ATD, methimazole treatment was further increased (maximum dose reached 25 mg/day = 0,51 mg/kg/day) and combined with levothyroxine (0.5 μg/kg/day), with an initial partial benefit.

However, due to the further difficulty of achieving normal thyroid hormone homeostasis and the persistence of clinical manifestations with important worsening struma (left lobe 25 × 25 × 56 mm; right lobe 25 × 26 × 58 mm), one year after the initial diagnosis it was decided to perform radical treatment by total thyroidectomy.

In the postoperative period, the boy had no clinical or biochemical features of hypoparathyroidism or laryngeal nerve injury and was discharged with thyroid replacement therapy (levothyroxine 50 μg/day).

Histological analysis of the removed tissue revealed papillary thyroid micro-carcinoma (2.8 mm), staged pT1a, with no indications for radioiodine treatment after surgery.

The boy is currently in follow-up at our department for clinical, biochemical and hormonal monitoring. Weakness and asthenia are not longer referred, final height had already been reached at the first evaluation but postoperative BMI improved to 17.8 kg/m^2 6 months after surgery and 18.4 kg/m^2 one year after the intervention. One year after surgery, the thyroid hormonal profile with the levothyroxine replacement therapy is adequate, no relapse of the disease was found at ultrasound.

Discussion

Graves' disease is a rare condition in children, but it is the most common cause of hyperthyroidism in this age group [1, 2].

Clinical and biochemical control of Graves' disease with the medical treatment alone is not always achievable, with a remission rate of about 30% in children treated with ADT [1, 2]. Therefore, the treatment of Graves' disease in childhood is still under discussion, especially with regards to the duration of ATD therapy and the timing of radical treatment. ATD treatment withdrawal is recommended after two years, if negative TRAb, while long-term ATD treatment, for 4–10 years, in case of disease recurrence or positive TRAb titration. After 10 years of ATD treatment or when children are symptomatic with poor metabolic control, radical treatment should be considered [1, 2].

Herein we described a case report of a 16-years old male with Graves' disease who received definitive surgical treatment one year after the initial diagnosis. The ATD dosage was often adjusted over the course of the year without achieving long-lasting normalization of the thyroid hormone profile. The decision for definitive therapy was taken due to the state of hyperthyroidism and persistence of symptoms, worsening struma and the frequent need for laboratory evaluations. Histological analysis following total thyroidectomy revealed papillary thyroid microcarcinoma, without prior evidence of thyroid nodules on ultrasound control. The importance of ultrasound monitoring of patients with Graves' disease has been remarked considering the high probability of nodule detection before definitive therapy, even if, as in the presented case, microcarcinoma is not detectable at ultrasound evaluation [7]. Similarly to other cases reported in the Literature, radioiodine treatment has not been performed for thyroid carcinoma and there are no signs of disease recurrence one year after total thyroidectomy. Finally, the reported patient's quality of life and BMI improved considerably after definitive surgical treatment.

Recent studies have shown a higher risk of cancer in adult patients with hyperthyroidism and thyroid nodules [3, 4]. In patients with Graves' disease, the likelihood of thyroid cancer increases in the presence of one or more thyroid nodules at ultrasound imaging, with a cancer risk rate of 22% compared with 5.1% in the absence of nodules [3]. To date there are few data on the co-presence of Graves' disease and DTC in children and adolescents [3–7].

Compared to adults, thyroid cancer in childhood has a frequent extra-thyroid localization and expecially thyroid nodules with unknown significance or without diagnostic definition have a higher rate of malignancy [8]. This consideration is particularly valid when considering childhood cancer survivors, a particular group of subjects with a higher risk for hyperthyroidism and thyroid cancer since childhood [9–10].

When ultrasound examination reveals thyroid nodules associated to Grave's disease, fine needle agobiopsy (FNAB) should be performed to guide the further approach.

In adults with GD, DTC does not appear to be associated with more aggressive behavior, the same behavior currently seems to be present also in pediatric age or when compared with children or adolescents with only DTC [6].

However, considering the higher malignancy of thyroid cancer in the paediatric age, rigorous and accurate monitoring of GD is necessary given the higher risk of developing thyroid

cancer, as well as a tailored decision on case-by-case basis on the duration of therapy with ATD and on the timing of any radical treatments, taking into account all possible risk factors, especially in childhood cancer survivors.

Finally, considering the greater aggressiveness of thyroid malignancies in childhood compared to adults, in the case of surgical treatment it is preferable to adopt a total thyroidectomy rather than a near-total one.

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