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Case Report

Papillary Thyroid Carcinoma in a Pediatric Patient With β-Thalassemia

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Abstract

β-Thalassemia is characterized by the abnormal synthesis of β-hemoglobin chains resulting in hemolytic anemia. Treatment involves frequent blood transfusions, which leads to deposition of iron in many organs, including endocrine glands. To date, several cases of papillary thyroid cancer (PTC) in patients with β-thalassemia have been reported in the adult literature, but there have been none in pediatrics. Here we report on an female adolescent with β-thalassemia who initially presented for evaluation of secondary amenorrhea. On examination, her thyroid gland was asymmetric, firm in consistency, with palpable lymph nodes along the right anterior cervical chain. A thyroid ultrasound revealed an enlarged right lobe containing 3 focal hypoechoic masses with calcific foci. Biopsy was consistent with PTC. She underwent total thyroidectomy and histological examination confirmed the diagnosis. Her postoperative course was uncomplicated and she was started on replacement therapy with levothyroxine. This is the first reported case of PTC in a pediatric patient with β-thalassemia. The incidence of thyroid cancer in patients with β-thalassemia is currently unknown; however, there may be utility in routine surveillance of this patient population.

Key Words: pediatric endocrinology, thyroid carcinoma

Abbreviation: PTC, papillary thyroid carcinoma/cancer.

Introduction

β-Thalassemia is a hereditary blood disorder caused by deficient synthesis of the β-globin subunit of hemoglobin [1]. Individuals with β-thalassemia major have severe hemolytic anemia that requires frequent blood transfusions and lifelong multidisciplinary medical care [2]. Repeated blood transfusions lead to iron overload and subsequent deposition of iron in many organs, including endocrine tissue such as the thyroid gland [3]. The increasing use of iron chelation therapy has allowed for improved quality of life and life expectancy in patients who require repeated transfusions [2] . Nonetheless, complications, including malignancy, continue to be observed in this patient population. We describe the first reported pediatric patient with β-thalassemia who developed papillary thyroid carcinoma (PTC).

Case Presentation

A 15-year 4-month-old female was referred to pediatric endocrinology by her hematologist for evaluation of secondary amenorrhea. The patient had experienced menarche at age 13 years 4 months and had thelarche 2 years prior. She had been experiencing amenorrhea for 11 months. Her medical history was notable for β-thalassemia for which she had received blood transfusions every 2 to 3 weeks since age 5 months. She underwent a laparoscopic splenectomy at age 10 years. She had received iron chelation with deferasirox; however, she developed acute pancreatitis, transaminitis, and Fanconi-like syndrome and was subsequently transitioned to deferiprone. For more than a year prior to referral her ferritin levels had been stable at less than 1500 ng/mL (3370 pmol/L) (reference range, 10-120 ng/mL; 22-270 pmol/L).

Diagnostic Assessment

On initial physical examination, the patient's height was at the 15th percentile, weight at the fifth percentile, and body mass index at the 12th percentile. She was Tanner IV for pubarche and Tanner V for thelarche. She was noted to have a prominent and asymmetric thyroid gland. On palpation the right thyroid lobe was firm and there was right anterior cervical lymphadenopathy. There were no obvious discrete nodules. Laboratory evaluation for causes of secondary amenorrhea was unremarkable, including thyroid function tests (Table 1). Thyroid ultrasound revealed an enlarged right thyroid lobe; measuring a calculated volume of 5.9 mL compared to 2 mL for the left lobe. Three hypoechoic masses with irregular borders and internal calcific foci were identified in the right lobe (Fig. 1). The patient underwent a fine-needle aspiration biopsy that showed atypical follicular cells with enlarged nuclei, intranuclear cytoplasmic pseudoinclusions, and psammoma bodies, consistent with PTC. Additional imaging revealed iron deposition in her pancreas, liver, kidneys, bone marrow and pituitary gland (Fig. 2). Given the pituitary iron deposition, her luteinizing hormone, prolactin, insulin-like growth factor 1, and adrenocorticotropin were assessed and found to be within normal limits for her age (see Table 1).

Treatment

The patient underwent a total thyroidectomy with central compartment neck dissection. The final pathology revealed

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Table 1. Laboratory investigations at presentation

	Value	Reference range
IGF-1	163 ng/mL (21.31 nmol/L)	127-554 ng/mL (16.6-72.43 nmol/L)
Prolactin	15.2 ng/mL (15.2 µg/L)	1.40-24.0 ng/mL (1.40-24.0 ug/L)
TSH	2.252 uIU/mL (2.252 mIU/L)	0.400-4.200 uIU/mL (0.400-4.200 mIU/L)
Thyroxine, free	0.95 ng/dL (12.2 pmol/L)	0.80-1.50 ng/dL (10.3-19.3 pmol/L)
Luteinizing hormone	2.1 mIU/mL (2.1 IU/L)	0.4-11.7 mIU/mL (0.4-11.7 IU/L)
Thyroglobulin antibody	<1.0 IU/mL	0.0-0.9 IU/mL
Thyroglobulin	17.6 ng/mL (17.6 ug/L)	3.0-30.4 ng/mL (3.0-30.4 ug/L)
ACTH	18.7 pg/mL (4.1 pmol/L)	7.2-63.3 pg/mL (3.8-13.9 pmol/L)
Fructosamine	271 umol/L (0.271 mmol/L)	0-285 umol/L (0-0.285 mmol/L)
PTH	13pg/mL (1.38 pmol/L)	10-65 pg/mL (1.06-6.89 pmol/L)
ALT	24 U/L	1-45 U/L
AST	26 U/L	1-35 U/L

Abbreviations: ACTH, adrenocorticotropin; ALT, alanine transaminase; AST, aspartate transaminase; IGF-1, insulin-like growth factor 1; PTH, parathyroid hormone; TSH, thyrotropin.

T1N0 right PTC. Postoperatively she was started on replacement therapy with levothyroxine 75 mcg daily (1.6 mcg/kg/day).

Outcome and Follow-up

The patient was closely followed by the otolaryngology, endocrinology, and hematology departments. She was noted to have persistently detectable thyroglobulin levels, with negative thyroglobulin antibodies, and an iodine uptake scan revealed a thyroid remnant. She underwent radioactive iodine 131 ablation therapy at 11 months postoperatively. At 2 years postoperatively a thyroglobulin level of 14.7 ng/mL (14.7 µg/L) (reference range, 1.5-38.5 ng/mL; 1.5-38.5 µg/L) was detected on routine screening. Her thyroglobulin antibodies remained negative. Fine-needle aspiration biopsy was consistent with recurrent PTC, and she underwent a right selective neck dissection.

Discussion

Malignancy, particularly hematologic malignancy and hepatocellular carcinoma, has been documented to occur with increased frequency in individuals with thalassemia [1]. Additionally, the incidence of thyroid carcinoma in thalassemia has been found to be higher than in the general population [4]. In 2011, Poggi et al [5] described the first 2 cases of thyroid cancer in adult patients with β-thalassemia. Govoni et al [6] also reported

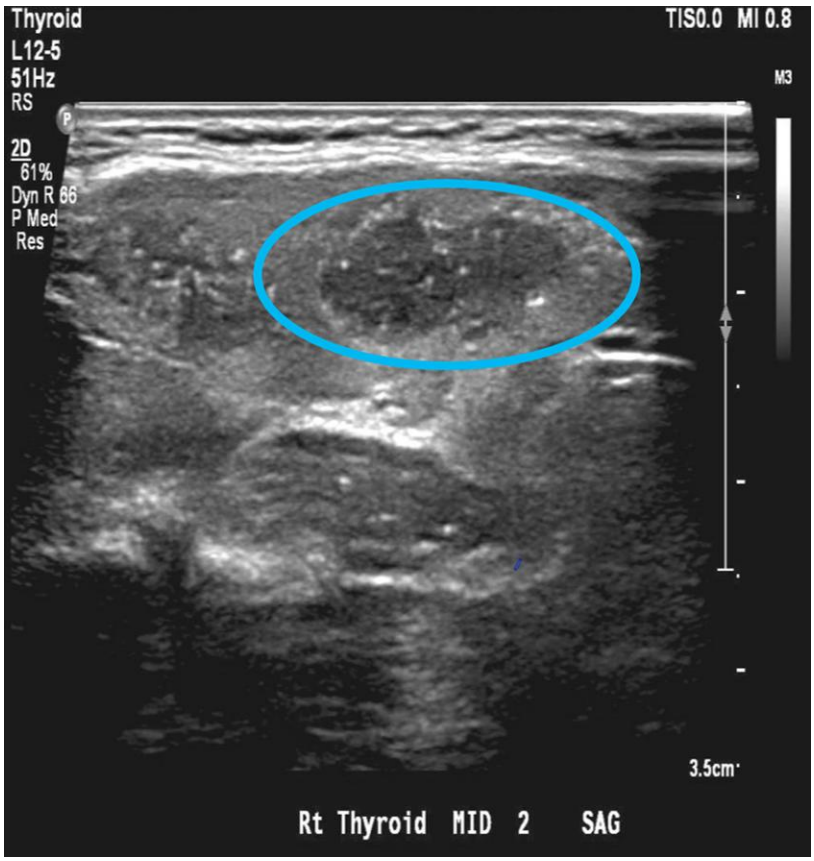

Figure 1. Ultrasound imaging shows a thyroid nodule with irregular borders and containing a myriad of tiny, brightly echoic echogenic foci concerning for calcifications.

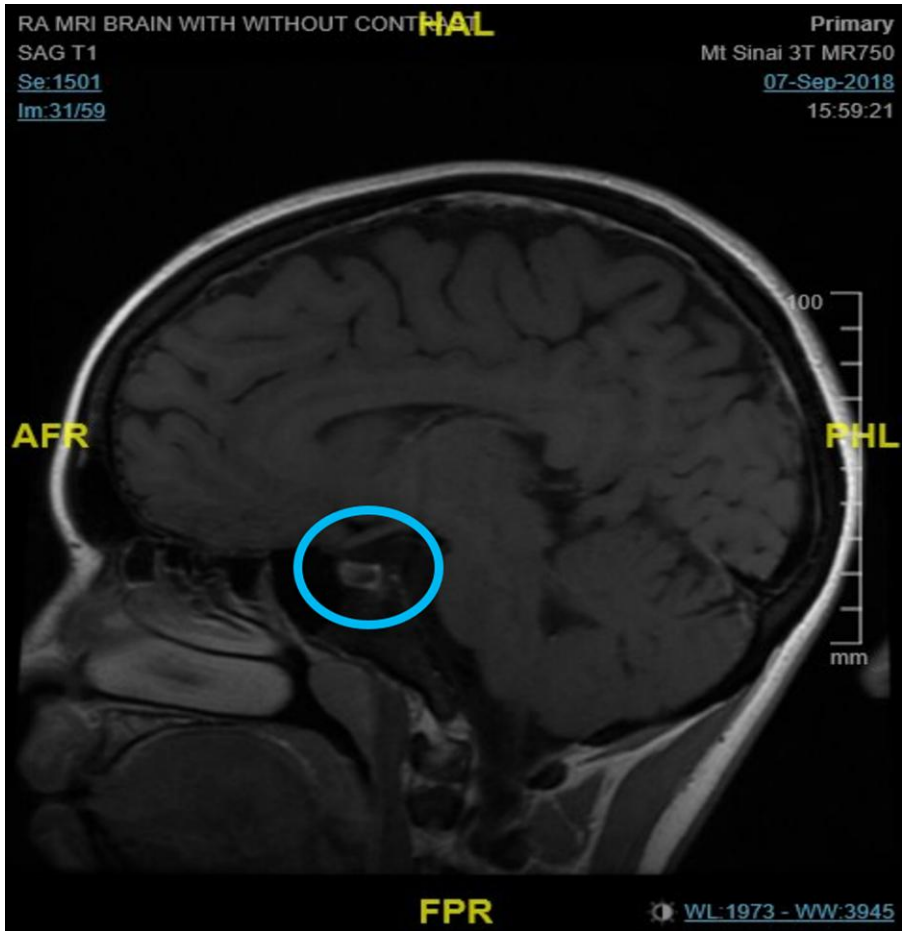

Figure 2. Brain magnetic resonance imaging scan shows a prominent hypointense signal throughout the pituitary gland, suggesting iron deposition in the setting of chronic anemia and recurrent transfusions.

that in an adult cohort of patients with β-thalassemia, 5 of 16 patients with thyroid nodules turned out to have PTC. In a review De Sanctis et al [4] surveyed 18 international centers for complications in patients with thalassemia. They determined 0.41% of adults with thalassemia had thyroid papillary and follicular carcinoma. It has been speculated that iron overload, specifically through the production of oxygen free radicals, is the causative mechanism for neoplasm development [1]. Naithani et al [7] examined the levels of free radical markers in pediatric patients with β-thalassemia and found an increase in levels of malondialdehyde, nitric oxide, and superoxide dismutase compared to controls. These markers significantly correlated with serum ferritin levels. It has also been hypothesized that an overabundance of iron can lead to alteration of cytokine activity and suppress the tumoricidal action of macrophages [3]. Generally, these processes occur over time, so resultant complications are seen later in life.

Endocrine complications, including hypogonadism, short stature, hypoparathyroidism, diabetes mellitus, and hypothyroidism, have been widely documented in pediatric patients with β-thalassemia [4]. These complications are also largely attributed to iron overload. The spectrum of pubertal disorders in patients with β-thalassemia is wide, ranging from delayed pubertal onset to hypogonadism. In such cases pubertal induction, either with oral estrogen in females or intramuscular testosterone in males, is recommended [8]. In addition to iron deposition in the liver and pituitary leading to defects in the growth hormone–insulin-like growth factor 1 axis, malnutrition, psychosocial stress, and chronic anemia are postulated to contribute to the pathogenesis of growth failure in these patients [9]. Decreased growth velocity and short stature have been treated with recombinant human growth hormone therapy with variable results in this population [8, 9]. Iron-mediated damage to the thyroid gland can result in hypothyroidism. The 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-Dependent Thalassemia recommend laboratory screening for thyroid dysfunction annually after age 9 years [9]. However, there are currently no standardized recommendations for screening for thyroid cancer in this patient population.

Before the use of blood transfusions, patients with thalassemia died within the first decades of life. The introduction of frequent transfusion and chelation therapy into mainstream management of these patients has resulted in substantially increased life expectancy. Nonetheless, even with the introduction of iron chelation into mainstream therapy, endocrine side effects are prominent. To improve the quality of life and long-term outcomes for these patients, routine screening for complications is recommended. Given the prevalence of endocrine complications in this patient population, we recommend annual screening for endocrine disorders in pubertal and postpubertal children by physical and/or biochemical evaluation.

Learning Points

- Endocrinopathies are common in patients with β-thalassemia.
- Thyroid malignancy may be associated with treatment methods for hemolytic anemia.
- Pediatricians should be aware of risk of endocrinopathies in patients requiring frequent blood transfusions.

Contributors

L.C. and M.W. were involved in the diagnosis and management of this patient and manuscript submission. Both authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient, now >18 years old.

Data Availability Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

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