FREQUENCY OF THYROID NODULES IN PATIENTS WITH β -THALASSEMIAS IN SOUTHERN IRAN

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Abstract

Background. Although thyroid nodules are a common finding in the general population, determining the clinically important nodules is essential. We investigated thyroid nodules or cysts by thyroid ultrasonography (US) in patients with β -thalassemia major (β -TM) and intermedia (β -TI). We also report a β -TI patient who was diagnosed with thyroid cancer six months before our screening.

Methods. In this cross-sectional study, 178 patients with β -thalassemias referred to the Thalassemia Clinic in a tertiary hospital affiliated to Shiraz University of Medical Sciences were investigated, from January to June 2016, by US.

Results. Thyroid nodules or cysts were detected in 11 patients [total: 6.17 %; 8 patients with β -TM (8.2%) and 3 patients with β -TI (3.7%)]. All nodules were < 1 cm in diameter and were not suspicious of malignancy. All patients, after 1 year of thyroid US follow-up, did not show any significant change in favor of malignancy.

Conclusion. Based on our results, the frequency of thyroid nodules was similar to what was reported in the general population. However, a long-term follow-up of these patients is recommended because of the potential carcinogenic effects of iron and hepatitis C infection (HCV). To achieve more precise information, collaborative multicenter studies should be considered.

Key words: β -thalassemias, thyroid cancer, thyroid nodules.

INTRODUCTION

β -thalassemias are a group of the most common genetic anemias characterized by a decrease or absence of β -globin chain production resulting in variable phenotypes ranging from the carrier state to the severe transfusion-dependent type (1). As a result of the improvement of management, the quality of life

and life-expectancy of these patients has increased in the past four decades. Today in developed countries, survival of patients with β -thalassemias major (β -TM), on conventional treatment, has increased to 40–50 years; it is also expected in the near future to extend it further (2).

Parallel to the significant amelioration of the main clinical features of the disease, adult patients suffer from complications that affect the heart, liver, bones and endocrine glands, requiring special health care by specialists (2, 3). Furthermore, the possibility of occurrence of other diseases such as malignancies, considered rare in the past, are currently increasing opening new scenarios for oncoming years. The most common reported cancers are hepatocellular carcinoma (HCC), hematologic malignancies (4-12), and thyroid cancer (13-15). In a recent multicentre survey, the prevalence of thyroid papillary and follicular carcinoma was 0.41% (15). The highest prevalence was registered in Greece and Italy (1.3% and 1.5%, respectively), followed by Oman (1.0%) (15).

Because thyroid nodules are a common finding in the general population, the major challenge for the clinician taking care of patients with thalassemia is to determine which of these nodules are clinically important (16, 17).

Ultrasonography (US) is the gold standard for study of thyroid nodules. It can detect small, multiple nodules and lateral neck lymphadenopathies. US is also important to select those nodules which should be subjected to fine needle aspiration cytology (FNAC).

The primary aim of the study was to detect thyroid nodules or cysts by US in a group of patients with β -TM and β -thalassemia intermedia (β -TI). In addition, we report a patient with β -TI and thyroid

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cancer who had been diagnosed earlier than our screening period. To the best of our knowledge this is the first case of thyroid cancer reported in patients with β -TI in southern Iran.

MATERIAL AND METHODS

In this cross-sectional study, 178 patients with β -thalassemias above the age of 12 years (97 patients with β -TM and 81 patients with β -TI) were evaluated from a total of 700 β -TM and 300 β -TI, followed at the Thalassemia Centre hospital, affiliated to Shiraz University of Medical Sciences in southern Iran.

All patients were selected by the systematic random sampling method from January to June 2016.

Patients with a family history of thyroid cancer, Hashimoto's disease or functional thyroid disease at the time of screening, a history of unknown thyroid diseases, or a history of hereditary disease, including multiple endocrine neoplasia (MEN) type I and IIa, surgery or radiation therapy for thyroid disorders were excluded from the present study.

Mean of serum ferritin (SF) levels, in the last six months, as well as liver iron concentration (LIC) were registered from their medical records.

The manufacturer's normal reference range values for SF were 30–350 ng/mL in males, and 15–150 ng/mL in females. LIC was expressed in mg Fe/g weight. Four classes of LIC have been reported in thalassemic patients: Class 1=normal LIC < 3.2 mg Fe/g dry liver, Class 2=mild overload LIC 3.27 mg Fe/g dry liver, Class 3=moderate LIC overload 7–15 mg Fe/g dry liver, and Class 4=severe LIC overload ≥ 15 mg Fe/g dry liver (18).

High resolution US examination of the thyroid was performed in supine position with a Samsung UGEO WS80A, equipped with a 7.5-10.0 MHz linear transducer. Thyroid volume, position, structure, echogenity, and the presence of pathologic structures (such as nodules, cysts, and congenital abnormalities) were evaluated.

Nodules or cysts were classified into three categories designated as: A, B and C (19). Category A was further divided into two categories, A1 for those without nodules or cysts, A2 for those with nodules smaller than 5.0 mm and/or cysts smaller than 20 mm; Category B: >5.1 mm nodules and/or > 20.1 mm simple or colloid cysts, and Category C subjects requiring immediate examination due to a finding of a large or suspicious thyroid tumour/lymph node. Subjects in category B were recommended to undergo the next round of TU examination one year later.

The thyroid nodules detected in this study were analysed according to their type (solid, cystic or mixed), echogenicity ("hyperechoic", "isoechoic", "hypoechoic" and "marked hypoechoic"), margins (lobulated or irregular margins), shape and evidence of calcifications. Mixed cystic-solid nodules were considered as 'nodules. When calcifications were present they were classified as microcalcifications (<1 mm) and macrocalcifications (calcific foci more than 1 mm with acoustic shadowing) (20).

Vascularity was evaluated by Color Doppler US and classified as absent, peripheral or central. When enlarged cervical lymph nodes were present they were categorized as benign or malignant according to their shape and hilum. Thyroid pseudonodules, which are encountered frequently in thyroiditis, were not counted as nodules.

According to the European Thyroid Association guidelines for US malignancy risk stratification of thyroid nodules in adults (20), at least 1 of the following features was considered to have a high suspicion of malignancy: irregular shape, irregular margins, microcalcifications (<1mm, most often round calcification), marked hypoechoic (and solid).

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences (Grant number: 10553). Informed written consent was obtained from all patients or their legal guardians. Demographic, clinical and laboratory data including age, sex, and age of starting blood transfusion were collected by a designed questionnaire.

Statistical analysis

Data were analyzed by statistical package for the social sciences (SPSS) software (SPSS Inc., Chicago, Illinois, USA) version 23. Descriptive data were presented as mean, standard deviation and percentages. Fisher exact test was used to compare qualitative variable between two groups. P value less than 0.05 was considered statistically significant.

RESULTS

Overall, mean age of the patients was 29 ± 6.9 years (range: 13-54 years), including 105 females (59%) and 73 (41%) males. Table 1 summarizes the demographic and laboratory data of studied population. Thyroid nodules (Category A2, B) were detected in 8 patients with β -TM (8.2%) and 3 patients with β -TI (3.7%), with no statistically significant difference between the two groups (P: 0.214).

Characteristics of nodules are presented in Table 2. In seven out of 11 thalassemic patients nodules or cysts were found in the right thyroid lobe. All nodules were smaller than 1 cm in diameter and none of them was suspicious for malignancy. Patients with nodules were followed for one year without any significant change in favor of malignancy development.

About 33.3% of patients, with nodules or cysts, had moderate or severe iron overload based on LIC assessment compared to 34.4% of patients without nodules. The difference between the two groups was not statistically significant ($P > 0.999$).

Thyroid cancer was diagnosed about six months earlier than our screening, in a 26-year-old female β -TI patient. The diagnosis of β -TI was done

at the age of 5 years. Due to the low hemoglobin level, at the age of 10 years she received a single blood transfusion. Since the diagnosis she was taking hydroxyurea (HU:10 mg/kg/daily) and folic acid (5 mg daily), followed up to the age of 17 years by iron chelation therapy (Deferasirox, 10 mg/kg/day). Spleen size was enlarged (3 cm below costal margin). In May 2014, she became pregnant. During pregnancy, HU was discontinued and monthly blood transfusions were given. In the last month of pregnancy, she had fever, neck enlargement and difficulty in swallowing. Nodular goiter was detected at clinical examination.

A malignancy (Category C) was suspected by US (right nodule: 5×2×1 cm without calcification, left nodule: 1.5 ×1×1 cm) and was confirmed by FNAC.

Table 1. Demographic and laboratory data of patients with β -thalassemias

Variables	β -thalassemia major N=97	β -thalassemia intermedia N=81
Age (year)	26.5 $\pm$ 5.3	32.3 $\pm$ 7.4
Sex (female) - Number (%)	64 (66)	41 (50.6)
Age of starting transfusion (month)	8.5 $\pm$ 4.3	Occasional
Serum ferritin (ng/mL)	2702 $\pm$ 2593	631 $\pm$ 574
Liver iron content (LIC) expressed in mg Fe/g dry weight	Number (%)	Number (%)
Normal	24 (26.7)	13 (31.7)
Mild	29 (32.2)	20 (48.8)
Moderate	13 (14.4)	5 (12.2)
Severe	24 (26.7)	3 (7.3)

Table 2. Characteristics of thyroid nodules in patients with β -thalassemias

Age	Sex (M/ F)	Number of nodule/s	Location of nodule/s	Borders	Echogenicity	Calcifications	Increased intranodular vascularity	Nodule composition	Lymph node involvement	Size of nodules (mm)
24	M	1	Right lobe	well defined	mix	no	no	complex cystic	no	5 mm
25	M	1	Right lobe	well defined	anecho	no	no	cystic	no	3 mm
37	F	1	Left lobe	well defined	hypo echo	no	no	solid	no	1.3 mm
21	F	1	Right lobe	well defined	mix	Yes (>1 mm)	no	complex cystic	no	7.3 mm
35	F	1	Right lobe	well defined	hypo echo	no	no	solid	no	3.6 mm
30	F	2	Right lobe	well defined	mix	no	no	solid	no	6.1 mm 4.5 mm
29	M	1	Right lobe	well defined	hypo echo	no	no	solid	no	2 mm
47	M	1	Right lobe	well defined	hypo echo	Yes (>1 mm)	no	solid	no	5.5 mm
23	F	1	Right lobe	well defined	hypo echo	no	no	solid	no	2.9 mm
22	F	1	Left lobe	well defined	hypo echo	no	no	solid	no	2.5 mm
20	M	1	Left lobe	well defined	hypo echo	no	no	solid	no	4.6 mm

She underwent thyroidectomy 4 months after normal vaginal delivery. She gave birth a child in good health status. The histological report was compatible with a "papillary thyroid carcinoma (conventional), lymphocytic thyroiditis, cervical lymph node metastases, without invasion of thyroid capsule lymph, and blood vessels invasion". The patient underwent total thyroidectomy and lymph nodes lateral neck dissection.

In the early postoperative period, she was monitored for possible complications such as hypocalcemia and vocal cord paralysis. No complications were noted in the late postoperative period. After total thyroidectomy, the patient underwent one episode of radioactive iodine therapy (150 millicuries) and hormone replacement therapy with L-thyroxin (150 μ g, daily).

At the last examination, about two years after treatment, the thyroglobulin level was less than 0.040 ng/mL. Moreover, serum calcium, phosphorus and thyroid function were in the normal range, serum ferritin and hemoglobin level were 550 ng/mL and 9 g/dL, respectively.

DISCUSSION

In recent decades the incidence of thyroid cancer has increased steadily and consistently in many developed countries and several evidences show a close correlation between the incidence rate of thyroid cancer and rates of screening for thyroid cancer by US (21, 22). In the general population, the 5-year survival rate for thyroid cancer overall is 98.1% and it varies from 99.9% for localized disease to 55.3% for distant disease (23). The most common type of thyroid carcinoma is papillary thyroid carcinoma that has a good prognosis (24).

According to the literature, thyroid cancer represents the third cause of malignancy in patients with β -TM (4, 12, 14). Therefore, we evaluated thyroid US in a population of asymptomatic patients with β -thalassemias. Our patients did not report any exposure to radiation of the head and neck, did not suffer previous malignancies or being in an area with known environment risk factors. Overall, 6.1% of patients (8.2% in β -TM and 3.7% in β -TI) had thyroid nodules or cysts, smaller than 1 cm in diameter, with no significant signs and symptoms of malignancy.

Nodules were more prevalent in patients with β -TM compared to β -TI; however, the difference was not statistically significant.

Similar results were reported by Govoni *et al.* (13) in 195 patients with β -TM (16 thyroid nodules; 8.2%) and De Sanctis *et al.* (25). The latter authors performed a thyroid US, in addition to the periodic (6-12 months) assessment of FT4 and TSH, in all adult patients with thalassaemia, followed in two Italian centers. Thyroid nodules were found in 8.6% of 58 examined β -TM or β -TI patients.

In contrast to our results, a higher incidence of thyroid nodules was found by Baldini *et al.* in 31 out of 88 patients (35.2 %) with β -TM, who had positive family history of thyroid disease, thyroid or neck lymph node enlargement or hypothyroidism (26). Most of the detected nodules were smaller than 1 cm in diameter and no malignant cases were found. All patients with nodules were followed for a median period of 4 years without occurrence of any malignancy.

We speculate that the reported higher frequency of thyroid nodules could be due to several factors: different selection of patients, advanced patients' age and a more prolonged exposure to iron overload.

Although thyroid nodules were not more prevalent than the normal population (16, 17), Govoni *et al.* (12) found a papillary thyroid carcinoma (PTC) in 2 females and 3 males (31%), aged 32-57 years, with iron overload and hepatitis C infection (HCV).

Iron overload, due to the frequent blood transfusion, can have carcinogenic effect by oxidative damage, suppression of tumoricidal action of macrophages, and cytokine activities dysfunction (13, 15, 27, 28). An ontogenetic role for HCV has also been suggested by several clinical epidemiologic studies (13, 29). The potential oncogenic effect of viruses was further supported by Poggi *et al.* (14). A thyroid cancer was found in two female patients with β -TM (aged 36 years and 40 years), both HCV and HBV positive. In the first patient the serum ferritin value was 135 ng/mL (range from 60 to 262 ng/mL, in the past few years before she was diagnosed with thyroid cancer) and the value of LIC assessed by T2* was 1.3 mgFe/g d.w. In the second patient, the mean serum ferritin was 1200 ng/mL (range from 96 to 1500 ng/mL in the past few years before she was diagnosed with thyroid cancer) while the value of LIC, assessed by SQUID, was 5.2 mg Fe/g dw.

It should be highlighted that all of our patients with β -TI were non transfusion-dependent and only 20% had moderate to severe iron overload based on LIC assessment. Furthermore, in our screening, no case of thyroid cancer was detected. However, in one patient out of 300 with β -TI, followed in southern Iran, thyroid

cancer was reported. Unexpectedly, the affected patient was neither transfusion-dependent nor iron-overload or seropositive for HCV.

Similar results were reported by De Sanctis *et al.* (25) in a 24 year-old β -TI patient with serum ferritin of 272 ng/mL and negative serology for HCV and HBV.

One of the limitations of our study was the limited size of the sample. Furthermore, US criteria to differentiate between benign and malignant thyroid nodules have been the point of research in many papers; many of the published papers proved that US is highly sensitive but less specific in detection of malignant thyroid nodules. However, in our patients thyroid US features for prediction of malignancy were not present and no increase in size or evidence of the clinical progression, was observed, after one year of follow up. However, the long-term outcomes of patients with benign thyroid nodules have been evaluated scarcely.

One large single-center study with a mean follow-up time of 8.5 years found a low rate of new diagnosis of thyroid cancer (30). An Italian, multicentre study also found a low rate of new diagnosis of thyroid cancer; however, only about half of the patients had undergone FNAC (31).

In addition, MRI T2- weighted imaging signal intensity ratio (SIR) or diffusion coefficients (ADCs) values can potentially provide quantitative information to separate papillary thyroid carcinomas PTC from benign thyroid nodules (32, 33).

In conclusion, the frequency of thyroid nodules in patients with β -TM was similar to what reported in the general population and all of them were non-malignant. In a 26-year-old female with β -TI PTC was documented. Because this patient had no major risk factors such as iron-overload and HCV infection, other unknown causes must be considered. To achieve more precise results, collaborative multicentre studies should be considered.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Taher AT, Cappellini MD. How I manage medical complications of β -thalassemia in adults. *Blood*. 2018;132(17):1781-1791.
2. De Sanctis V, Elsedfy H, Soliman AT, Elhakim IZ, Soliman NA, Elalaily R, Kattamis C. Endocrine profile of β -thalassemia major patients followed from childhood to advanced adulthood in a tertiary care center. *Indian J Endocrinol Metab*. 2016;20(4):451-459.
3. Fica S, Albu A, Vladareanu F, Barbu C, Bunghez R, Nitu L, Marinescu D. Endocrine Disorders In β -Thalassemia Major: Cross-Sectional Data. *Acta Endocrinol (Buchar)*. 2005;1(2):201-212.
4. Benetatos L, Alymara V, Vassou A, Bourantas K. Malignancies in β -thalassemia patients: a single-center experience and a concise review of the literature. *Int J Lab Hematol*. 2008;30(2):167-172.
5. Otroek ZK, Shamseddine AI, Taher AT. Non-Hodgkin disease in β -thalassemia major. *Am J Hematol*. 2006;81(1):62-64.
6. Sallam MM, Alsuliman AM, Alahmed HE, Alabdulaali MK. Chronic myelogenous leukemia in sickle cell/beta 0-thalassemia. *Indian J Pathol Microbiol*. 2011;54(3):597-598.
7. Thapa R, Pal PK, Mukhopadhyay M. Beta thalassemia major and hodgkin lymphoma. *J Pediatr Hematol Oncol*. 2009;31(6):462-463.
8. Tozzi-Cecchetti MC, D'Amelio R, Baroni CD. Thalassemia major terminating in a non-Hodgkin B-cell lymphoma: report of a case. *Tumori*. 1979;65(3):353-357.
9. Chehal A, Loutfi R, Taher A. β -Thalassemia intermedia and non-Hodgkin lymphoma. *Hemoglobin*. 2002;26(3):219-225.
10. Alavi S, Safari A, Sadeghi E, Amiri S. Hematological malignancies complicating β -thalassemia syndromes: a single center experience. *Blood Res*. 2013;48(2):149-151.
11. Karimi M, Giti R, Haghpanah S, Azarkeivan A, Hoofar H, Eslami M. Malignancies in patients with β -thalassemia major and β -thalassemia intermedia: A multicenter study in Iran. *Pediatr Blood Cancer*. 2009;53(6):1064-1067.
12. Zanella S, Garani MC, Borgna-Pignatti C. Malignancies and thalassemia: a review of the literature. *Ann N Y Acad Sci*. 2016;1368(1):140-148.
13. Govoni MR, Sprocati M, Fabbri E, Zanforlin N, De Sanctis V. Papillary thyroid cancer in thalassaemia. *Pediatr Endocrinol Rev*. 2011;8 Suppl 2:314-321.
14. Poggi M, Sorrentino F, Pascucci C, Monti S, Lauri C, Bisogni V, Toscano V, Cianciulli P. Malignancies in β -thalassemia patients: first description of two cases of thyroid cancer and review of the literature. *Hemoglobin*. 2011;35(4):439-446.
15. De Sanctis V, Duran Canatan D, Tzoulis P, Daar S, Di Maio S, Elsedfy H, Yassin MA, Filosa A, Soliman N, Karimi M, Saki F, Sobti P, Kakkar S, Christou S, Albu A, Christodoulides C, Kilinc Y, Al Jaouni S, Khater D, Alyaarubi SA, Lum SA, Campisi S, Anastasi S, Galati MC, Raiola G, Wali Y, Elhakim IZ, Mariannis D, Ladis V, Kattamis C. An ICET-A survey on occult and emerging endocrine complications in patients with β -thalassemia major: Conclusions and recommendations. *Acta Biomed*. 2019; 89(4):481-489.
16. Bojunga J. Ultrasound of Thyroid Nodules. *Ultraschall Med*. 2018;39(5):488-511.
17. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. *Ann Intern Med*. 1997;126(3):226-231.
18. Pierre TGS, Clark PR, Chua-anusorn W, Fleming AJ, Jeffrey GP, Olynyk JK, Pootrakul P, Robins E, Lindeman R. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. *Blood*. 2005;105(2):855-861.
19. Suzuki S, Yamashita S, Fukushima T, Nakano K, Midorikawa S, Ohtsuru A, Yasumura S, Hosoya M, Kamiya K, Shimura H. The protocol and preliminary baseline survey results of the thyroid ultrasound examination in Fukushima [Rapid Communication]. *Endocr J*. 2016;63(3):315-21.
20. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *Eur Thyroid J*. 2017;6(5):225-237.
21. Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"-screening and overdiagnosis. *N Engl J Med*. 2014;371(19):1765-1767.
22. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst*. 2010;102(9):605-613.

23. National Cancer Institute. Cancer stat facts: thyroid cancer. <https://seer.cancer.gov/statfacts/html/thyro.html>. Accessed March 9, 2017.
24. Aslan A, Sancak S, Aslan M, Ayaz E, Inan I, Ozkanli SS, Alimoglu O, Yikilmaz A. Diagnostic value of duplex Doppler ultrasound parameters in papillary thyroid carcinoma. *Acta Endocrinol (Buchar)*. 2018;14(1):43-48.
25. De Sanctis V, Campisi S, Fiscina B, Soliman A. Papillary thyroid microcarcinoma in thalassaemia: an emerging concern for physicians? *Georgian Med News*. 2012;210:71-76.
26. Baldini M, Serafino S, Zanaboni L, Cappellini MD. Thyroid cancer in β -thalassemia. *Hemoglobin*. 2012;36(4):407-408.
27. Toyokuni S. Role of iron in carcinogenesis: cancer as a ferrototoxic disease. *Cancer Sci*. 2009;100(1):9-16.
28. Huang X. Does iron have a role in breast cancer? *Lancet Oncol*. 2008;9(8):803-807.
29. Ferri C, La Civita L, Zignego A, Pasero G. Viruses and cancers: possible role of hepatitis C virus. *Eur J Clin Invest*. 1997;27(9):711-718.
30. Nou E, Kwong N, Alexander LK, Cibas ES, Marqusee E, Alexander EK. Determination of the optimal time interval for repeat evaluation after a benign thyroid nodule aspiration. *J Clin Endocrinol Metab*. 2014;99(2):510-516.
31. Durante C, Costante G, Lucisano G, Bruno R, Meringolo D, Paciaroni A, Puxeddu E, Torlontano M, Tumino S, Attard M. The natural history of benign thyroid nodules. *JAMA*. 2015;313(9):926-935.
32. Noda Y, Kanematsu M, Goshima S, Kondo H, Watanabe H, Kawada H, Bae KT. MRI of the thyroid for differential diagnosis of benign thyroid nodules and papillary carcinomas. *AJR Am J Roentgenol*. 2015;204(3):W332-W335.
33. Shi R, Yao Q, Wu L, Zhou Q, Lu Q, Gao R, Hu J, Kao L, Bains A, Yan Z. T2* mapping at 3.0 T MRI for differentiation of papillary thyroid carcinoma from benign thyroid nodules. *J Magn Reson Imaging*. 2016;43(4):956-961.