

SHORT COMMUNICATION

MALIGNANCIES IN β -THALASSEMIA PATIENTS: FIRST DESCRIPTION OF TWO CASES OF THYROID CANCER AND REVIEW OF THE LITERATURE

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□ *β -Thalassemias are a group of hereditary blood disorders characterized by abnormalities in the synthesis of the β hemoglobin (Hb) chains. This disease causes excessive storage of iron in all organs and endocrine glands. Treatment of β -thalassemia major (β -TM) consists of regular blood transfusions, iron chelation and management of secondary complications of iron overload. Endocrine abnormalities are frequently observed. In the last 25 years, the clinical picture of the disease has changed progressively thanks to improvement of treatments. Today, the majority of thalassemic patients reach adult age. The better prognosis and the longer lifespan of affected patients could be responsible for the susceptibility to other concomitant diseases which can manifest during their life. In this context, the possibility and recent literature reports about some cases of malignancy in thalassemic patients open new scenarios for oncoming years. We describe first reports of endocrine malignancies in thalassemic patients.*

Keywords Thalassemia, Thyroid Cancer, Iron, Endocrine neoplasia

β -Thalassemia major (β -TM) is a hereditary disease characterized by an impaired production of hemoglobin (Hb) chains which can be due to more than 200 mutations of the β chain genes. These mutations induce an abnormal production of the same Hb and cause a severe hemolytic anemia. The main therapy is a regular transfusion regimen that is responsible for

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iron deposition and excessive storage (1). The possibility of an adequate chelation therapy has dramatically improved the quality and the expectation of life for these patients (2). Nowadays, these patients have the chance to survive until adult age. Moreover, the clinical picture of this disease has changed in comparison with the past.

The iron deposition, secondary to this treatment, causes a cytotoxic effect in many organs including the endocrine glands. Endocrine complications represent one of the most relevant problems and, specifically, alterations of pituitary, adrenal, thyroid, pancreatic and bone are the most important (3,4).

The improvement in life expectancy also provides the possibility that these patients suffer from pathologies of older decades of life-like malignancies. Moreover, iron deposition could be responsible for progressive cell damage that can result in neoplastic induction and progression. Liver fibrosis and cirrhosis increase the risk of hepatocellular carcinoma. To date, there are few descriptions of malignancies in thalassemic patients. Moreover, the contemporary presence of many clinical conditions and the complexity of treatment administered, make these patients more complicated to manage and call for a more precocious and efficient approach.

CASE REPORTS

Patient 1 was a 36-year-old female who came to our attention 1 year ago. She was affected by β -TM diagnosed at the age of 18 months because of pallor and growth retardation. She has received regular red blood cell transfusions since then. She underwent a splenectomy during her late teens and her serological tests were positive for hepatitis C virus (HCV) and negative for hepatitis B virus (HBV) and human immunodeficiency virus (HIV).

She was given chelating therapy with deferoxamine (DFO) and achieved excellent results (the last serum ferritin value was 200 mg/dL). The mean serum ferritin value in the past few years before she was diagnosed with thyroid cancer was 135 mg/dL (range from 60 to 262 mg/dL). The value of liver iron concentration (LIC) assessed by T2* was 1.3 mgFe/gdw.

Her endocrinological history consisted of hypogonadism, diagnosed for growth and pubertal retardation and treated with estroprogestins per os since she was 18 years old; osteoporosis treated with calcium and vitamin D, and hypothyroidism. The impaired thyroid function was incidentally discovered many years before during a routine serological evaluation, and for this reason the patient has been taking l-tiroxine (Eutirox[®], 50 mcg/day; Bracco, Milan, Italy) replacement therapy since then with good results, both in clinical signs and symptoms and in serological results.

The patient's thyroid morphological study, performed by ultrasonographic examination 10 years ago, revealed a multinodular goiter. She

underwent a two fine-needle aspiration (FNA) biopsy some years before, which were inconclusive (not diagnostic for cells scarcity) and since then a strict follow-up has been conducted yearly. She arrived at our department, and because of a slight increase of the bigger nodule in the ultrasonographic evaluation, we decided to perform another FNA. The cytological examination showed the presence of a differentiated multifocal classic papillary thyroid cancer. The patient was sent to surgery to undergo a total thyroidectomy in February 2010.

The histological report was as follows: "Two parts of thyroid: one of these of 12 g weight and 4×4×5 cm, the other of 25 g weight completely constituted by a nodule of 4 cm in diameter. In the second part the solid yellow-earth nodule with cystic plots. Focal area of metaplasia with Hurthle cells. The tumor is multifocal with variably sized complex papillary structures lined with cells with increased nuclear/cytoplasmic ratios and apically placed nuclei that produced a surface bulge (hobnail appearance)."

The definitive histological report stated: "Papillary thyroid classic multifocal carcinomas of right and left lobes of thyroid, the maximum diameter is 2.88 mm. The cancer is limited inside of thyroid capsule. Vascular and lymphatic invasion (big and small blood vessels): absent. The rest of the gland showed a microfollicular hyperplasia with focal Hurthle cells metaplasia. pTNM (based on AJCC VII ed 2010): pT1; pNx; pMx." After the thyroidectomy the patient was sent to the department of Nuclear Medicine to undergo radiometabolic therapy with ¹³¹I.

The post-surgery period was uneventful and she is in a good general condition. She is taking triiodothyronine replacement therapy (Titre®; Teofarma, Pavia, Italy) 40 mcg/day and is waiting for the radionuclide treatment. We encouraged her to continue the medical therapy and to have a serological, ultrasonographic and clinical evaluation every 6 months.

Patient 2 was a 40-year-old female suffering from β-TM. She was diagnosed at the age of 3 months, and treated with regular red blood cell transfusions since then and chelating therapy with DFO. The mean serum ferritin value in the past few years before she was diagnosed with thyroid cancer was 1200 ng/mL (range from 96 to 1500) while the value of LIC, assessed by SQUID, was 5.2 mgFe/gdw. She underwent splenectomy at 18 years old and her serological tests were positive for HCV and HBV and negative for HIV.

Her endocrinological history comprises a previous diagnosis of hypogonadism, for failure of pubertal growth, and bone demineralization discovered in previous bone densitometry measurement performed by means of dual X-ray photon absorptiometry (DEXA). For these reasons she takes replacement therapy with estroprogestinic (per os) and antirisorbitive therapy with bisphosphonates in association with additional doses of calcium and vitamins D.

Ten years ago she complained of the sudden appearance of a nodule on the right side of the neck. An ultrasonographic thyroid study was performed which showed the presence of a thyroid nodule. A thyroid scintigraphic study showed that the nodule was cold and so an FNA biopsy with cytology evaluation was performed. The result was positive for the presence of neoplastic cells and surgery was advised.

A total thyroidectomy was performed and histological examination revealed a Follicular variant of papillary thyroid cancer. The histological report was as follows: "Right thyroid lobe of mm 35×20×7 plus two parts of 23 and 20 mm of diameter, respectively. The weight is 4.5 g. Surface is irregular, colloid looking. There is a focus of Follicular variant of papillary thyroid cancer of 7×4 mm size. The left lobe of thyroid is of 45×20 cm with a weight of 7 g. Irregular surface with a whitish tumour with a maximum diameter of 30 mm. Extensive infiltration of neoplastic cells with characters of sclerosant variant of papillary thyroid cancer primarily solid. There are many psammomatous bodies, fibrous areas and large peritumoral lymphatic permeable. The remaining part of thyroid looks like colloid. The histological report of enclosed preparation inside paraffin confirmed the intra-operating diagnosis of metastatic lymphonodes."

A radiometabolic therapy with ^{131}I was performed (1100 MBq). Since then the patient has been taking replacement therapy with l-tiroxine (current dosage 150 mcg/day, Eutirox[®]; Bracco). She is in good health and the last examination did not show any signs of residual or recurrent disease (neck ultrasonographic evaluation is negative and thyroglobulin level is undetectable).

β -Thalassemia major is one of the most common genetic disorders in the world. It is a common health problem in many geographic areas such as the Mediterranean region, in the Middle East, Africa, the Indian subcontinent and Southeast Asia. It is a hereditary disease characterized by severe anemia resulting from defects in β -globin synthesis that cause a shortened erythrocyte lifespan.

The life expectancy of thalassemic patients has greatly increased since the introduction of iron chelation in the late 1970s. In fact, more than half of the thalassemic patients were expected to be alive at the age of 40 years. As the lifespan of these kind of patients increased, malignancies become manifest (5–7). In recent years, some investigators have reported the association of some malignancies, especially in the liver and hematopoietic system (8), and thalassemia. It has not yet been established whether the coexistence of two severe diseases (cancer and thalassemia) is a coincidence or if there is a link between the two pathological entities.

We know, from *in vitro* studies, that iron overload has been associated with various mechanisms capable of inducing carcinogenic transformation.

In fact, some studies showed that severe iron overload could produce significant production of oxygen-free radicals (9). In turn, oxidative damage can give rise to a neoplastic clone through genetic or epigenetic alterations. Moreover, iron overload can induce carcinogenesis *via* suppression of the tumoricidal action of macrophages and alteration of cytokine activities (10,11). Most important, a recent randomized trial, showed that iron reduction by phlebotomy decreased cancer risk in a supposedly normal population (12). It is not yet clear if these aspects are also involved in the exposition to transfusion-transmitted infections caused by bacteria, parasites and viruses such as HBV, HCV, HIV, human herpes virus and cytomegalovirus (13). In fact, all these viruses can play a role in B-cell lymphomagenesis. Finally, of great relevance in the onset of malignancies, a role can be played by the administration of chelating therapy (14). Some reports showed that DFO can exert a protective effect through its action on cell cycle control molecules and on nuclear factor- κ B (NF- κ B). Moreover, DFO seems to have a protective effect against the oxygen radicals and proto oncogene expression. The influence of DFO on angiogenic processes and the role of other chelating agents is not yet clear (15).

From a clinical point of view, iron overload has been associated with various malignancies, such as liver, hematological, colorectal, kidney, lung, mammary and stomach cancer (16,17). In the last 10 years, the literature reports nearly 50 cases of malignancies (Table 1) that arose in patients affected by thalassemia (major or intermedia). The most frequent are malignancies of liver and blood (18–20). No cases of thyroid cancer in patients affected by β -TM have been reported as yet.

To the best of our knowledge, these are the first two cases described. Thyroid cancer is a relatively rare problem that accounts for nearly 1% of all malignancies. The annual incidence varies considerably in different registries ranging from 1.2 to 2.6 per 100,000 individuals in men and from 2.0 to 3.8 per 100,000 in women (21). Our unit has more than 100 patients affected by β -TM. The presence of the above two cases is over the expected prevalence and could be a warning for the future.

We would like to emphasize two aspects. The first one is iron, as in other malignancies in thalassemia and the above report. Also in thyroid cancer, recent reports seems to underline the significance of iron overload. In a recent article (22), thyroid cancer incidence is higher in the region of Sicily where levels of elements (like manganese and iron) in the drinking water often exceeded maximum admissible concentrations. Our patients showed good levels of serum ferritin and LIC, as the result of a good chelation therapy regimen.

The second is the prognosis of this kind of cancer. In the general population this is, generally, very good. We do not know if in thalassemic

TABLE 1 Previous Reports on Thalassemic Patients Affected With Cancer Published in the Last 10 Years

Patients Reported	Hemoglobinopathy	Type of Cancer	Reference
1	β^S/β -thal	HD	Moschovi <i>et al.</i> , 2001 = 23
5	β^S/β -thal	MM	Kaloterakis, 2001 = 24
1	β -TI	NHL	Chelal, Loutfi, Taher, 2002 = 25
1	β -TM	CML	Voskaridou <i>et al.</i> , 2002 = 26
23	β -TM; β -TI; β^S/β -thal	HCC	17
1	β -TM	cardiac NHL; tonsil NHL	Ricchi <i>et al.</i> , 2004 = 27
1	β -TM	HCC	Mancuso <i>et al.</i> , 2005 = 28
1	β -TI	HD	Jabr <i>et al.</i> , 2006 = 29
1	β -TM	NHL	18
3	β -TM; β -TI	Se(?); NHL, HD	5
10	β -TM; β -TI	NHL; HD; CML	8
9	β -TM; β -TI	HCC	Maggio, 2010 = 30

β^S/β -thal; Hb S/ β -thalassemia; HD; Hodgkin disease; MM; multiple myeloma; β -TI; β -thalassemia intermedia; NHL; non Hodgkin lymphoma; β -TM; β -thalassemia major; CML; chronic myeloid leukemia; HCC; hepatocellular carcinoma.

patients, thyroid cancer also maintains its good biological behavior. We should certainly keep in mind some implications that make these patients more difficult to manage. In fact, tiroxine suppressive therapy, the main approach after surgery (21) in people affected by thyroid cancer, could result in worse bone and cardiac status that are often altered in thalassemic patients.

Surely it does not seem possible to make conclusive judgements about these two aspects. What we can say is that the occurrence of malignancies in patients affected by β -thalassemia, major and intermedia, could be an emerging concern for physicians. Once more, thalassemia syndromes seem like a great challenge for physicians in the future. The great incidence in some areas of the world, the important presence of migration fluxus toward our country from areas where the prevalence of thalassemia is endemic, and the difficulty of treating some new emerging pathologies are to follow and treat these patients with caution, and only where a multi disciplinary approach with a skilled dedicated team is provided.

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REFERENCES

1. Rund D, Rachmilewitz E. β -Thalassemia. *N Engl J Med.* 2005;353(11):1135–1146.
2. Angelucci E, Barosi G, Camaschella C, *et al.* Italian Society of Hematology practice guidelines for the management of iron overload in thalassemia major and related disorders. *Haematologica.* 2008;93(5):741–752.

3. De Sanctis V. Multicentre study on prevalence of endocrine complications in thalassaemia major. *Clin Endocrinol (Oxf)*. 1995;42:581–588.
4. Borgna-Pignatti C, Cappellini MD, De Stefano P, *et al.* Survival and complications in thalassemia. *Ann NY Acad Sci*. 2005;1054:40–47.
5. Benetatos L, Alymara V, Vassou A, Bourantas KL. 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.
6. Wasniewska M, Raiola G, Teresa A, *et al.* Gynecomastia disclosing diagnosis of Leydig cell tumour in a man with thalassemia, secondary hypogonadism and testis microlithiasis. *Acta Biomed*. 2009;80(3):286–288.
7. Thapa R, Pal PK, Mukhopadhyay M. β Thalassemia major and Hodgkin lymphoma. *J Pediatr Hematol Oncol*. 2009;31(6):462–463.
8. Karimi M, Giti R, Haghpanah S, *et al.* Malignancies in patients with β -thalassemia major and β -thalassemia intermedia: a multicenter study in Iran. *Pediatr Blood Cancer*. 2009;53(6):1064–1067.
9. Naithani R, Chandra J, Bhattacharjee J, *et al.* Peroxidative stress and antioxidant enzymes in children with β -thalassemia major. *Pediatr Blood Cancer*. 2006;46(7):780–785.
10. Toyokuni S. Role of iron in carcinogenesis: cancer as a ferrototoxic disease. *Cancer Sci*. 2009;100(1):9–16.
11. Huang X. Does iron have a role in breast cancer? *Lancet Oncol*. 2008;9(8):803–807.
12. Zacharski LR, Chow BK, Howes PS, *et al.* Decreased cancer risk after iron reduction in patients with peripheral arterial disease: results from a randomized trial. *J Natl Cancer Inst*. 2008;100(14):996–1002.
13. Kaur P, Basu S. Transfusion-transmitted infections: existing and emerging pathogens. *J Post-Grad Med*. 2005;51(2):146–151.
14. Richardson DR. Potential of iron chelators as effective antiproliferative agents. *Can J Physiol Pharmacol*. 1997;75(10–11):1164–1180.
15. Jiao Y, Wilkinson J 4th, Di X, *et al.* Curcumin, a cancer chemopreventive and chemotherapeutic agent, is a biologically active iron chelator. *Blood*. 2009;113(2):462–469.
16. Joosten E, Meeuwissen J, Vandewinckele H, Hiele M. Iron status and colorectal cancer in symptomatic elderly patients. *Am J Med*. 2008;121(12):1072–1077.
17. Borgna-Pignatti C, Vergine G, Lombardo T, *et al.* Hepatocellular carcinoma in the thalassaemia syndromes. *Br J Haematol*. 2004;124(1):114–117.
18. Otrrock ZK, Shamseddine AI, Taher AT. Non-Hodgkin disease in β -thalassemia major. *Am J Hematol*. 2006;81(1):62–64.
19. Kontoghiorghes GJ (Guest Ed). Proceedings of the 17th International Conference on Chelation (ICOC) for the Treatment of Thalassemia, Cancer and Other Diseases Related to Metal and Free Radical Imbalance and Toxicity. November 2007, Shenzhen, China. *Hemoglobin*. 2009;33(5):283–397.
20. Restivo Pantalone G, Renda D, Valenza F, *et al.* Hepatocellular carcinoma in patients with thalassemia syndromes: clinical characteristics and outcome in a long term centre experience *Br J Haematol*. 2010; 150(2):245–247.
21. Sherman SI. National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology, Thyroid Cancer V.1. 2009 (http://www.nccn.org/professionals/physician_gls/PDF/thyroid.pdf).
22. Pellegriti G, De Vathaire F, Scollo C, *et al.* Papillary thyroid cancer incidence in the volcanic area of Sicily. *J Natl Cancer Inst*. 2009;101(22):1575–1583.
23. Moschovi M *et al.* “Hodgkin’s disease in a child with sickle cell disease treated with hydroxyurea.” *Pediatr Hematol Oncol* 2001; 18 (6): 371–6.
24. Kaloterakis *et al.* “Multiple myeloma in sickle cell syndromes” *Haematologia* 2001; 31 (2): 153–9.
25. Chehal A *et al.* “Beta-thalassemia intermedia and non-hodgkin’s lymphoma” *Hemoglobin* 2002; 26 (3): 219–25.
26. Voskaridou *et al.* “Chronic myeloid leukaemia with marked thrombocytosis in a patient with thalassaemia major: complete haematological remission under the combination of hydroxyurea and anagrelide” *Br J Haematol* 2002; 116 (1): 155–7.
27. Ricchi *et al.* - “Asymptomatic cardiac lymphoma in a hepatitis C virus-positive thalassemic patient” *Ital Heart J* 2004; 5 (4): 302–4.

28. Mancuso *et al.* - "Hepatocellular carcinoma on cirrhosis-free liver in a HCV-infected thalassemic" *Am J Hematol* 2005; 78 (2): 158-9.
29. Jabr *et al.* - "Beta-Thalassemia intermedia and Hodgkin lymphoma" *Am J Hematol* 2006; 81 (2): 151.
30. Maggio *et al.* - "Hepatocellular carcinoma in patients with thalassemia syndromes: clinical characteristics and outcome in a long term single centre experience" *Br J Haematol* 2010; 150 (2): 245-7.

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