

# Graves' thyrotoxicosis in a patient with metastatic differentiated thyroid carcinoma and chronic lymphocytic leukaemia (CLL)

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## Abstract

Thyrotoxicosis is rare in patients with thyroid carcinoma. A case is reported of a 66-year-old woman with Graves' disease, papillary thyroid carcinoma (PTC) with pulmonary metastases and chronic lymphocytic leukaemia (CLL). After thyroidectomy and antithyroid drug (ATD) withdrawal, thyrotoxicosis recurred. Treatment with ATD and <sup>131</sup>I (six doses, 36.3 GBq in total) resulted in permanent hypothyroidism and significant destruction of lung metastases. The course of CLL was mild, but transient anaemia and thrombocytopenia were observed after <sup>131</sup>I therapy. Pathomechanisms of thyrotoxicosis in patients with metastatic thyroid carcinoma, its treatment and its relation to CLL are presented.

**Key words:** thyroid carcinoma, thyrotoxicosis, metastases, radioiodine therapy, chronic lymphocytic leukaemia.

## Introduction

Thyrotoxicosis, resulting from hyperfunctioning metastases of differentiated thyroid carcinoma (DTC), is a rare finding, with only 71 cases reported in the medical literature [1-25]. It may occur when either TSH receptors, present on DTC cells, are stimulated by thyrotropin receptor-stimulating antibodies (TRAb), or metastases are bulky and thus capable of producing large amounts of thyroid hormones [1-16, 18-25]. The third, rare possibility is cancer, in which an activating TSH receptor mutation constitutively stimulates the cAMP cascade, which finally results in increased production of thyroid hormones [17].

Chronic lymphocytic leukaemia (CLL) is well known to be associated with autoimmune phenomena. These are most often related to the haematopoietic system but other autoimmune disorders, such as rheumatoid arthritis, pernicious anaemia, myasthenia gravis and Graves' disease, have also been reported in patients with CLL [26-31].

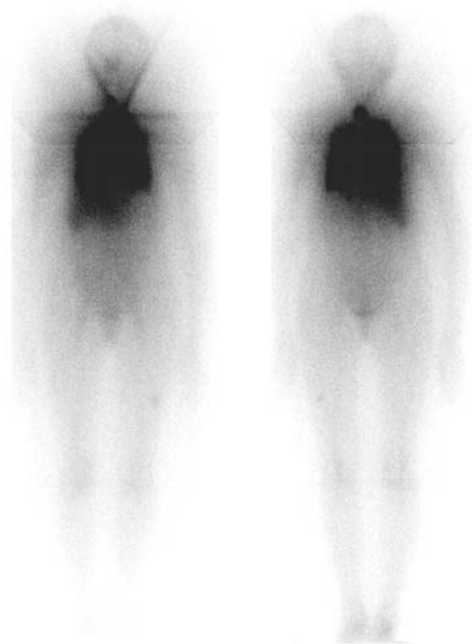
We report a case of Graves' disease with pulmonary metastases of DTC, causing severe thyrotoxicosis. Moreover, concomitant CLL was diagnosed in the same patient. Possible relationships of both disorders and the management of such cases are discussed.

## Case report

A 66-year-old woman was referred to our Department of Nuclear Medicine and Oncological Endocrinology in January 2004 for thyroid remnant ablation by means of  $^{131}\text{I}$ . Earlier, for three years, she had been treated with antithyroid drugs (ATD) for hyperthyroidism. Thyroid scintigraphy was not performed during ATD treatment. In September 2003, after fine needle aspiration biopsy of a slowly growing, but large (maximum dimension of 8 cm), nodule of the right thyroid lobe (fine needle biopsy



**Figure 1.** Chest X-ray with multiple, macronodular lung metastases



**Figure 2.** Whole body scan after the administration of  $^{131}\text{I}$  for thyroid remnants ablation (left – anterior view, right – posterior view). Intensive accumulation of  $^{131}\text{I}$  in both lungs

diagnosis of "papillary thyroid carcinoma" – PTC), the patient was referred for total thyroidectomy. On chest X-ray, taken before the operation, pulmonary metastases were documented (Figure 1), which were subsequently diagnosed – by transthoracic biopsy – as metastases of PTC. Another unexpected finding, discovered prior to thyroidectomy, was high leukocyte count (WBC –  $25.3 \times 10^3/\mu\text{l}$ ) with predominance of small, mature lymphocytes (94%) and presence of smudge cells. Examination of bone marrow aspirate showed 33.6% of all nucleated cells to have been lymphoid. Based on those findings, the diagnosis of chronic lymphocytic leukaemia (CLL) was established. The patient underwent total thyroidectomy in the middle of September 2003. Microscopic examination (including immunohistochemistry) of resected tissues confirmed the earlier suspicion and, finally, follicular and partially solid variant of PTC with vascular invasion was diagnosed in the right thyroid lobe. The left thyroid lobe consisted of benign nodules. After surgery, therapy with ATD was not restarted; nor was therapy for CLL administered. On admission to our Department, three months after thyroidectomy, the patient complained of weakness, easy fatigability, excessive sweating and recent weight loss. She did not report any history of radiation therapy; nor was there any family history of thyroid or blood disease. Her resting heart rate was 100 beats/min, the lungs were clear, neither cervical nor peripheral lymph nodes were palpable, and no abdominal organomegaly was observed. She had mild anaemia with marked lymphocytosis and normal platelet count (details regarding laboratory data and main therapy are reported in Table I). Markedly elevated free thyroxine ( $\text{FT}_4$ ) and free triiodothyronine ( $\text{FT}_3$ ) with TSH suppression confirmed the clinical suspicion of thyrotoxicosis with serum anti-TSH receptor antibodies (TRAb) elevated at 4.1 IU/l (normal values:  $<1.0$  IU/l, TRAK human RIA, BRAHMS, Berlin, Germany). Radioiodine uptake in the neck after 24 h was 2.3%. Scintigraphy after test dose of  $^{131}\text{I}$  demonstrated its uptake in the neck and extensive tracer uptake in the lungs. An ultrasound study of the neck revealed only remnants of both thyroid lobes (total volume of both remnants – around 4.5 ml) without enlarged lymph nodes. The diagnosis of thyrotoxicosis resulting from the stimulation by specific antibodies of TSH receptors within thyroid remnants and thyroid carcinoma lung metastases was obtained, and intensive ATD treatment was administered. After 2 weeks of treatment with thiamazole, the patient was euthyroid and, at the end of January 2004, she received 6.1 GBq of  $^{131}\text{I}$ . The post-treatment whole body scan (WBS), performed 7 days later, showed radioiodine uptake in thyroid remnants and intensive tracer accumulation in both lungs (Figure 2). The findings were then better visualised by a CT scan, which revealed multiple,

Table I. Summary of the main laboratory data and of the therapy course in the presented case

Date	TSH <sup>1</sup> [mIU/l]	FT <sub>4</sub> <sup>2</sup> [pmol/l]	FT <sub>3</sub> <sup>3</sup> [pg/ml]	Tg <sup>4</sup> [ng/ml]	TRAb <sup>5</sup> [IU/l]	Exogenous Tg recovery <sup>6</sup> [%]	aTg <sup>7</sup> [IU/ml]	Blood tests	Comment
05.01.2004	0.06	51.3	9.2	6.1	4.1	100	21	Hb – 10.1 g/dl WBC – 22.5 x 10 <sup>3</sup> /μl PLT – 206 x 10 <sup>3</sup> /μl Diff-Lymph. – 81%	Recurrent thyrotoxicosis diagnosed, ATD for 2 weeks, no therapy for CLL
26.01.2004		8.8	3.1						Treatment with 6.1 GBq <sup>131</sup> I, ATD begun 02.2004
20.04.2004	21.0	3.5	1.2	349.0	1.8	99	20	Hb – 9.2 g/dl WBC – 2.9 x 10 <sup>3</sup> /μl PLT – 118 x 10 <sup>3</sup> /μl Diff-Lymph. – 38%	ATD withdrawn prior to treatment with 7.4 GBq <sup>131</sup> I; after <sup>131</sup> I ATD not restarted, no L-T <sub>4</sub> therapy
31.08.2004	0.72			784.6		98		Hb – 10.9 g/dl WBC – 5.0 x 10 <sup>3</sup> /μl PLT – 50 x 10 <sup>3</sup> /μl Diff-Lymph. – 65%	Prednisone 30 mg/d
29.09.2004	0.03	17.6		354.0		99		Hb – 13.6 g/dl WBC – 26.0 x 10 <sup>3</sup> /μl PLT – 61 x 10 <sup>3</sup> /μl Diff-Lymph. – 79%	Treatment with 5.5 GBq <sup>131</sup> I, suppressive therapy with L-T <sub>4</sub> begun
5.04.2005	33.7			228.7	2.2	96	27	Hb – 12.0 g/dl WBC – 8.7 x 10 <sup>3</sup> /μl PLT – 85 x 10 <sup>3</sup> /μl Diff-Lymph. – 74%	Treatment with 7.4 GBq <sup>131</sup> I, prednisone 10 mg/d
11.10.2005	50.7	3.3	1.0	32.3	1.9	96	46	Hb – 11.6 g/dl WBC – 9.6 x 10 <sup>3</sup> /μl PLT – 66 x 10 <sup>3</sup> /μl Diff-Lymph. – 79%	Treatment with 8.0 GBq <sup>131</sup> I, prednisone 10 mg/d
04.04.2006	25.6			48.6	2.3	95	51	Hb – 12.3 g/dl WBC – 13.6 x 10 <sup>3</sup> /μl PLT – 79 x 10 <sup>3</sup> /μl Diff-Lymph. – 79%	Treatment with 8.0 GBq <sup>131</sup> I, prednisone 5 mg/d

<sup>1</sup>TSH reference range: 0.3–5.0 mIU/l; <sup>2</sup>FT<sub>4</sub> reference range: 11.0–23.0 pmol/l; <sup>3</sup>FT<sub>3</sub> reference range: 2.2–5.0 pg/ml; <sup>4</sup>Tg test functional sensitivity: 0.3 ng/ml; <sup>5</sup>TRAb normal values: <10 IU/l; <sup>6</sup>exogenous Tg recovery reference range: 80–120%; <sup>7</sup>aTg normal values: <100 IU/ml

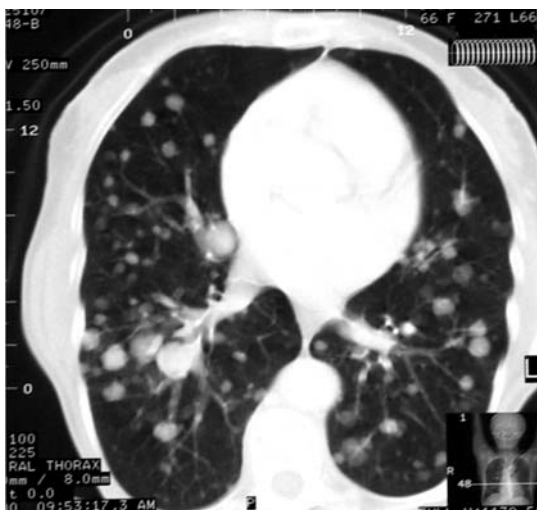


Figure 3. Chest CT, showing multiple lung metastases

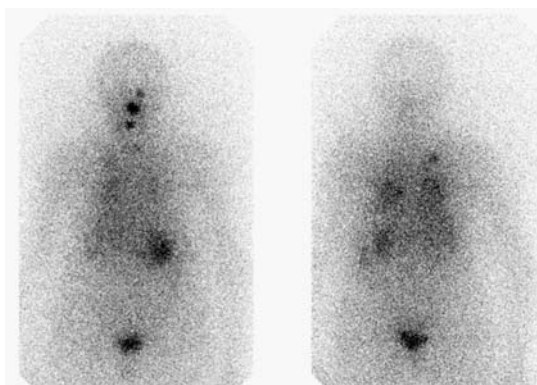


Figure 4. Whole body scan after the sixth therapeutic dose of <sup>131</sup>I (left – anterior view, right – posterior view)



Figure 5. Chest X-ray after the sixth therapeutic dose of <sup>131</sup>I

bilateral, macronodular metastases (Figure 3). At the follow-up visit (mid-February, 3 weeks after <sup>131</sup>I therapy) the patient was still euthyroid but ATD treatment was restarted (methimazole 10 mg/day). Three months later the patient was hypothyroid and (after stopping ATD) the second radioiodine

dose (7.4 GBq) was administered (April 2004). The post-treatment WBS, performed 4 days after therapy, showed both uptake in the neck (6.1% of administered activity) and in the lungs (11.6% of administered activity). Levothyroxine suppressive therapy was not begun after <sup>131</sup>I. At that time, the patient had moderate anaemia and leukopenia, with normal differential count, and no therapy for CLL was instituted. In late August 2004, a consulting haematologist suggested prednisone therapy (30 mg/d) for thrombocytopenia (platelets –  $50 \times 10^3/\mu\text{l}$ ). At the end of September 2004, when the patient was admitted for the third radioiodine treatment, she was clinically euthyroid. Only weak activity was detected in the neck and intense uptake of radioiodine in both lungs in post-therapeutic WBS. After therapy, TSH suppression with levothyroxine was begun. In April 2005, the fourth therapeutic dose of <sup>131</sup>I (7.4 GBq) was administered after endogenous TSH stimulation and radioiodine uptake of decreased intensity in the neck and in the lungs was demonstrated in post-therapeutic WBS. The platelet count was under control by means of prednisone at the dose of 10 mg/d (platelets –  $85 \times 10^3/\mu\text{l}$ ). In October 2005 and in April 2006, two subsequent therapeutic activities of around 8.0 GBq of <sup>131</sup>I each were administered after endogenous TSH stimulation. Only lung, but not neck, radioiodine uptake was visible on post-therapy scans (Figure 4). On chest X-ray images, only discrete, small, nodular lesions were detected (Figure 5). Blood cell count remained stable on low dose prednisone therapy – 5 mg/d. Further therapy is planned to be administered in several months.

## Discussion

Thyrotoxicosis, resulting from hyperfunctioning metastases of DTC, is a very rare entity [1-25]. Coexisting Graves' disease is the most likely cause of this disorder (as in our case), out of the three possible causes underlying thyrotoxicosis in patients with metastatic DTC (listed above).

We used a second generation anti-TSH-receptor antibodies assay, which is a highly specific test to diagnose Graves' disease, and we may believe that, in the case of our patient, anti-TSH receptor antibodies were indeed responsible for the stimulation of both the thyroid gland and the metastatic tissue in the lungs [32, 33]. Moreover, TSI (the main component of anti-TSH receptor antibodies detected in our assay, as demonstrated in several groups of patients with Graves' disease) are likely to be responsible for the initiation and progression of cancer growth [33-35]. It is even more interesting and cannot be excluded that the progression of thyroid carcinoma was, in our patient, self-perpetuating – some authors suggest that a differentiated, aggressive, metastatic thyroid carcinoma can initiate an autoimmune reaction, leading to production of

autoantibodies and thus to hyperthyroidism [24, 36, 37]. The cause-effect relationship of Graves' disease and thyrotoxicosis is additionally complicated in our patient by the coexistence of CLL, which is known to produce autoimmune disorders in about 20% of cases [38]. Recently, Hall et al. proved that CLL cells predispose to haematological autoimmunity by acting as aberrant antigen-presenting cells [39]. It is also likely that a disordered regulatory T-cell function in CLL is involved in the autoimmune process [28]. Under these circumstances it can be hypothesised that CLL led to or, at least, facilitated the development of Graves' disease in our patient, though only a few patients with the coexistence of Graves' disease and CLL have been described in the literature [30, 40].

Thyrotoxicosis was reported mainly in patients with metastatic follicular thyroid carcinoma, and PTC causing thyrotoxicosis was documented much less frequently [4, 15]. We were able to find in the medical literature only one report of a patient with PTC and thyrotoxicosis attributable to thyroid stimulating immunoglobulin (TSI) [1]. It is of interest that in that as well as in our case, the metastases were limited to the lungs, while sparing the cervical lymph nodes, which are a much more common site of PTC metastases.

Therapy should, in such cases, be aimed at both treating thyrotoxicosis and eradicating neoplastic tissue. Both goals can be achieved by surgery, when feasible. In our patient, the former goal was initially achieved by means of antithyroid drugs and <sup>131</sup>I, but the latter target could be achieved only with radioiodine. The patient, originally with severe thyrotoxicosis, was prepared with ATD to prevent exacerbation of the disease after radioiodine and was subsequently given two doses of <sup>131</sup>I at a relatively short time interval, which temporarily suppressed thyroid hormone production, but only the third dose of radioiodine permanently eradicated thyrotoxicosis. Although, after six courses of radioiodine therapy, the patient still presents with viable neoplastic tissue, its volume is remarkably reduced. Other authors report similar, relatively favourable, course of the disease [15, 16].

Already after one dose of radioiodine, we observed bone marrow suppression to be more pronounced than in other cases of DTC treated at our Department. It has previously been reported that radiation dose to bone marrow in patients with hyperfunctioning DTC is greater than in patients without such metastases [20, 21]. Despite the risk of bone marrow suppression, we decided to follow the "high dose" radioiodine therapy scheme with the aim of curing the patient [41]. We have not performed bone marrow dosimetry of therapy activity of radioiodine, which is difficult in patients with high endogenous production of thyroxine [20]. Clinically significant peripheral blood changes are

reported to be rare, even in patients treated with high doses of radioiodine [42]. Although, in our patient, bone marrow, infiltrated by leukaemic lymphocytes and stifled in the production of normal blood elements, could be more susceptible to radiation, the suppression of its function was transient and clinically insignificant.

CLL is a malignancy not found to be associated with radiation, so we could not expect any deterioration of its course; it was, however, interesting to find temporarily decreased production of an abnormal clone of lymphocytes after therapy with radioiodine. This is concordant with the well-known finding that low-dose total-body irradiation can induce CLL remissions sufficient to reduce the manifestations of disease, though it does not appear to be superior to chemotherapy [43].

## Conclusions

In patients with bulky metastases of DTC and Graves' disease one should be aware of possible thyrotoxicosis even after total thyroidectomy. Patients with thyrotoxicosis resulting from metastatic DTC can be safely and effectively treated with radioiodine, even in advanced stages of DTC with coexisting disorders.

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