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Case Report

# R-CHOP-Associated Graves' Hyperthyroidism

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**Keywords**
R-CHOP · Rituximab · Graves' disease · Hyperthyroidism · Thyroid lymphoma · Hashimoto's thyroiditis

**Abstract**
Radiation-induced thyroid dysfunction following oncologic treatment is not uncommon, however limited literature data has been found on patients that underwent chemotherapy only. A change in thyrometabolic autoimmune status is also a rare entity. We present a case of newly diagnosed Graves' thyrotoxicosis following a successful R-CHOP (Rituximab, Cyclophosphamide, Doxorubicine, Vincristine and Prednisone) treatment in a patient with concurrent abdominal and thyroid diffuse large B-cell lymphoma (DLBCL). Following chemotherapy, PET CT showed resolution of FDG-avid thyroid nodule as well as no evidence of the thyroid mass on repeat ultrasound. Her thyroid function also normalized. During her follow-up visit, patient reported significant unintentional weight loss and persistent fatigue over the past couple months. Repeat laboratory evaluation revealed TSH 0.005 mIU/mL, FT4 6.73 ng/dL and thyroid stimulating immunoglobulin (TSI) 535 (ref <140%). She was started on methimazole followed by radioactive iodine therapy. This unique case of Graves' disease following R-CHOP treatment in patients with known Hashimoto's and thyroid lymphoma is one of the first to be reported in the literature. The swing of pendulum from Hashimoto's to Graves' disease is very uncommon. As clinicians, we need to continue monitoring for clinical and biochemical thyroid dysfunction in this subset of population.



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## Background

Primary hypothyroidism occurs in approximately 20–30% patients who had therapeutic neck radiotherapy and this usually appears within the first 5 years after radiotherapy [1, 2]. It is so well established that irradiation of the thyroid gland also increases the risk of Graves' disease, Graves' ophthalmopathy, thyroiditis, benign thyroid nodules and thyroid cancer, especially papillary thyroid cancer [1–3]. The etiology of radiation-induced thyroid dysfunction includes parenchymal cell damage, effects on vascular system and or auto-immune reactions [1–3]. There are reports, that after neck irradiation, Graves' disease (GD), an autoimmune disease may develop in patients previously being treated for hypothyroidism and interestingly one third of patients with Graves' hyperthyroidism had received thyroxine treatment before its onset [2]. Therefore thyroid hormone-replacement therapy in patients with hypothyroidism after irradiation of the neck does not always eliminate the risk of other thyroid abnormalities, including GD at a later date [4]. It is postulated that thyroiditis observed in Hodgkin's disease may be the result of immune regulation dysfunction.

Diffuse large B-cell lymphoma (DLBCL)-targeted chemotherapy has also been shown to alter thyroid function and antibody production [5]. Rituximab, a commonly used drug in combination with other chemotherapeutic drugs (combination of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisone (R-CHOP) in the treatment of B-cell lymphoma targets B-cell specific CD20 antigen. Rituximab has also been utilized for therapy in autoimmune disorder such as Graves' orbitopathy. Improvement in goiter size and a decrease in thyroid autoantibody levels have been demonstrated.

The development of GD in the background of Hashimoto's thyroiditis and coexisting thyroid lymphoma (large B-cell lymphoma (DLBCL)) following R-CHOP treatment is rarely seen. We are reporting a patient with B-cell lymphoma of the thyroid gland and Hashimoto's thyroiditis who developed GD following treatment with R-CHOP chemotherapy.

## Case Report

A 66-year-old woman with a history of Hashimoto's thyroiditis and thyroid nodules initially presented for fine needle biopsy (FNB). Patient had no symptoms of hypothyroidism or hyperthyroidism. Her initial TSH was 5.9 IU/L (ref 0.27–4.20) with FT4 1.2 ng/dL (ref 0.89–1.76) (Fig. 1A) and thyroperoxidase (TPO Ab) and thyroglobulin (TG Ab) antibodies were 18,290 IU/mL (ref 0–34) and >2,250.0 IU/mL (ref 0.0–0.9) (Fig. 1B), respectively. Additionally serum thyroid stimulating immunoglobulin (TSI) level was 88% (ref 0–139) and thyrotropin receptor blocking antibody (TBRAb) (Fig. 1B) was also in the normal range (<10%, ref <10). Physical examination revealed normal vital signs and patient had no evidence of thyroid orbitopathy. Examination of the thyroid gland confirmed a 2-cm right lower lobe thyroid nodule and a 6-cm left thyroid nodule almost replacing the left lobe. Thyroid ultrasound showed multiple thyroid nodules bilaterally with a dominant hypervascular left thyroid mass 5.9 × 2.7 × 4.4 cm (Fig. 2A) and a right lower lobe nodule 2.4 × 2.4 × 2.2 cm. Additionally an ultrasound of the neck confirmed bilateral abnormal cervical lymphadenopathy. FNB of the thyroid nodules revealed a population of large lymphocytes with irregular nuclei (Fig. 2B). Fluorescence in situ hybridization (FISH) revealed a translocation t(14;18), fusing the immunoglobulin heavy chain gene at chromosome 14q32 with BCL2 gene at chromosome 18q21.3. Positron emission tomography computerized axial scan (PET-CT) of the chest and abdomen revealed a large retroperitoneal and mesenteric soft tissue mass, measuring 16 × 14 cm in greatest trans-

axial dimension. The retroperitoneal mass encased the aorta and inferior vena cava as well as mesenteric vessels and both renal arteries. The mass also displaced the kidneys peripherally (Fig. 3A). She was diagnosed with stage-IVE diffuse large B-cell lymphoma (DLBCL) and underwent six cycles of R-CHOP chemotherapy. Patient also received subdiaphragmatic external radiation directed to the retroperitoneal mass. Following chemotherapy, and radiation therapy, PET-CT scan showed resolution of retroperitoneal mass, resolution of fluorodeoxy-glucose (FDG) avid thyroid nodule (Fig. 3B) as well as no evidence of thyroid nodules on repeat ultrasound. Following chemotherapy her thyroid functions normalized (serum TSH 3.9 IU/L and free T4 1.4 ng/dL). A moderate decrease in thyroid peroxidase Ab (range 8,432 to 11,288 IU/mL) and thyroglobulin Ab (range 1,268 to 1,600 IU/mL) were noted. Additionally TSI 88% and TBRAb <10% (ref <10) (Fig. 1B) continue to remain in the normal range. She remained euthyroid without any symptoms of hypo or hyperthyroid and her serum TSH and free T4 remained normal for the next 2 years (Fig. 1A). Additionally she had no evidence of lymphoma recurrence.

Two years later, patient reported significant unintentional weight loss and persistent fatigue over the past couple months. Physical examination revealed a heart rate of 120/min, fine tremors of outstretched fingers, and no thyroid orbitopathy. Thyroid was 40 g in size with no palpable nodules and deep tendon reflexes were brisk. Repeat laboratory testing revealed: TSH 0.005 IU/L, FT4 6.73 ng/dL and TSI 535% (Fig. 1A, B). Serum TBRAb was also mildly elevated (28%). TPOAb and TGAb levels were 7,976 and 1,088 IU/mL respectively (Fig. 1B). Additionally, an HLA DQB1*03 was positive. Further evaluation confirmed the diffuse large B-cell lymphoma (DLBCL) lymphoma was in remission. A thyroid uptake and scan showed diffuse uptake with no photopenic areas and the $I^{131}$ uptake was elevated (4 h: 61.0%, reference 5–15%, at 24 h 70.3%, reference 10–30%).

Since patient received CAT scan with iodine load she was treated with methimazole for 3 months and following this, the patient was treated with 19.4 millicuries of radioactive iodine for thyroid ablation. Following radioactive iodine treatment patient developed hypothyroidism and this was treated with levothyroxine (Fig. 1A). Patient remained euthyroid for the next 4 years and during these 4 years the lymphoma continues to remain in remission.

## Discussion

The etiology of GD is complex and influenced by several factors, including genetics [6]. Human leukocyte antigen (HLA) association with different autoimmune disorders, including GD and Hashimoto's thyroiditis, has been well described in the literature. Genetic linkage analysis has shown HLA correlation with GD. Specific HLA variants, including DQB1*03, are associated with GD [6]. Interestingly in our patient HLA testing confirmed DQB1*03. The exact pathogenesis of GD developing after chemotherapy including R-CHOP is not well defined. It is also well known that patients with hypothyroidism due to Hashimoto's disease may rarely subsequently evolve to Graves' disease with hyperthyroidism [7]. In some of these patients TSI may more active rather than TBRAb and this may possibly result in Graves' hyperthyroidism. We have measured both the TSI and TBRAb before the patient developed GD and both of these antibodies were negative prior to patient receiving chemotherapy. Thus the development of TSI in high titers along with the manifestations of Graves' hyperthyroidism following R-CHOP suggests that the chemotherapy in combination with rituximab is possibly responsible for precipitating GD in our patient although GD developing in the background of Hashimoto's thyroiditis cannot be completely ruled out.

Thyroid dysfunction including GD can also manifest after specific treatments for malignancy, including diffuse large B-cell lymphoma (DLBCL) [8–10]. Lymphoma treatment may include radiation and chemotherapy. Thyroid disease following radiation to the neck is a frequent problem in patients treated for Hodgkin's disease [1–3]. Radiation-induced damage to the thyroid affects parenchymal cell architecture, and may cause vascular destruction, and autoimmune reactivity [3]. Thyroid irradiation typically manifests as hypothyroidism and develops usually within 5 years after treatment [1–4]. There is an increased risk of GD after neck irradiation or in patients with a history of levothyroxine use. Hancock et al. [2] studied 1787 patients with Hodgkin's disease treated with radiation, radiation plus chemotherapy, or chemotherapy alone. These investigators observed that thyroid disease including GD following radiation to the neck is a frequent problem in patients treated for Hodgkin's disease. Interestingly there was no mention of any thyroid disorders, especially GD developing in patients treated with chemotherapy alone in this paper. In another report, the risk of developing thyroid abnormality 20 years after irradiation was high at 52% [2]. Our patient received subdiaphragmatic radiation as part of treatment to abdominal lymphoma and the thyroid gland was protected by shielding from radiation damage. Thus it is unlikely radiation has any effect on development of GD in our patient. However limited literature data are available regarding the development of thyroid disorders in patients with lymphomas who has undergone chemotherapy only. A change in thyroid autoimmunity in these groups of patients undergoing chemotherapy is also rare. The patient reported in the present case report received rituximab in addition to CHOP therapy. Although there is an association between HLA DQB1*03 and GD [6], it is unknown whether thyroid function is being affected by R-CHOP therapy in patients with specific HLA type. Kahara et al. [5] reported thyroid antibodies levels in Hashimoto's thyroiditis decreased after rituximab monotherapy for thyroid MALT syndrome lymphoma. In our patient we have noted a modest decrease in the levels of thyroid antibodies and normalization of TSH following R-CHOP therapy although this may have happened independent of R-CHOP therapy, as part of the natural course of Hashimoto's thyroiditis. Interestingly in our patient rituximab therapy apparently induced the development of GD with hyperthyroid manifestations along with elevated levels of TSI and TBRAb. Rituximab, the humanized chimeric anti-CD20 monoclonal antibody, represents a powerful tool for treating B-cell malignancies and is used for the treatment of relapsed or chemo refractory low-grade or follicular non-Hodgkin's lymphoma, including thyroid lymphoma [10]. Recent in-vitro studies have made significant contributions and have led to the development of effective treatment strategies to optimize patient response and this includes R-CHOP therapy which was used in our patient. However it is not clear whether rituximab by itself or rituximab in combination with other chemotherapy agents precipitated GD in our patient.

Several studies support the effects of Rituximab on B-cell depletion and on thyroid antibody production. In NOD.H-2h4 mice model exposed to sodium iodide-supplemented drinking water to induce spontaneous autoimmune thyroiditis, thyroid autoantibody responses could be reduced by B-cell depletion. Moreover, B-lymphocyte depletion in this murine study resulted in diminished B- and T-lymphocyte infiltration of the thyroid gland and this inhibited the development of spontaneous autoimmune thyroiditis [11]. Raterman et al. [12] reported a diabetic patient with hypothyroidism and rheumatoid arthritis developing hyperthyroidism 4 months after initiating rituximab therapy. Interestingly these authors reported serum TPO antibodies levels decreasing to undetectable levels after rituximab treatment. However these investigators did not measure TSI or TBRAb levels. In our patient there was indeed a modest decrease in TPO and TgAb levels following rituximab treatment. Auto-antibodies synthesized by infiltrating B cells in the thyroid gland directed against the TSH receptor are crucial in the

etiology of GD. Plasma cells from the bone marrow and cervical lymph nodes are also involved in the synthesis of these autoantibodies. Additionally anti-CD20 treatment could also interfere with the B-cell antigen-presenting role to T cells and thereby interfere with T-cell activities. Thus a promising treatment of GD would be the elimination of pre-B-lymphocytes as well as activated mature B-lymphocytes expressing CD 20 antigen. Several investigators have studied treatment of GD with rituximab [11]. Salvi et al. [cited in 11] studied a limited number of patients with GD and concluded that thyroid function was not affected by treatment with rituximab. El Fassi et al. [cited in 11] performed a prospective controlled trial in 20 patients and concluded that rituximab treatment may not be more efficacious compared with a full course of methimazole therapy in treating GD. Heemstra et al. [cited in 11] studied patients with relapsing GD and noted some patients responded to rituximab treatment.

Controversy exists about the effect of rituximab on TSI and TBRAb levels. No studies found a relationship between proportions of CD-20+ lymphocytes after rituximab treatment and TSI and TBRAb levels. Salvi et al. [cited in 11] observed no significant differences in TSI levels after infusion with rituximab, whereas Heemstra et al. [cited in 11] found a significant decrease in TBRAb levels after treatment with rituximab. El Fassi et al. [cited in 11] also found a decrease in TBRAb levels in patients treated with rituximab and methimazole compared with patients treated with methimazole alone, suggesting an alteration of the balance from stimulating into non-stimulating antibodies due to decreased production of stimulating antibodies. There is an ongoing clinical trial investigating the effectiveness of rituximab in patients with GD and these investigators also plan to study the relationship between TBRAb titer and thyroid hormone status and immune cellular response in relationship to disease outcome in young patients with Graves' hyperthyroidism.

Rituximab causes an immediate depletion of circulating B cells and this depletion lasts for four to six months, but may last for more than 24 months and pre-treatment levels of B cells will be reached after nine to 12 months [11]. Our patient reported here has possibly increased susceptibility to GD as shown by HLA antigen type and preexisting Hashimoto's thyroiditis. It is also interesting to note that in our patient the GD developed 24 months after rituximab therapy, the time required for recovery of B cells and it may be postulated that the resurgence of the B cell function in our patient with a preexisting susceptibility precipitated GD.

Different types of cancer immune checkpoint inhibitors have been approved recently and these include CTLA-4 monoclonal antibodies (as ipilimumab); anti-PD-1 monoclonal antibodies (as pembrolizumab and nivolumab); and anti-PD-L1 monoclonal antibodies (as atezolizumab, ivolumab, and durmalumab) [13–15]. The increased immune response induced by these agents leads to immune-related adverse events including endocrine gland dysfunctions such as hypophysitis, thyroid dysfunctions, adrenal insufficiency, and type 1 diabetes mellitus, and are usually irreversible in 50%. In particular, hypophysitis is the most frequent anti-CTLA-4-antibodies-related side effects, while thyroid abnormalities such as hypothyroidism, thyrotoxicosis, painless thyroiditis, or even thyroid storm are more frequently associated with anti-PD-1-antibodies. The combination of anti-CTLA-4-antibodies and anti-PD-1-antibodies is associated with about 30% of immune-related adverse events including endocrine gland dysfunctions. Interestingly Van Kooten et al. reported transient thyrotoxicosis developing in a patient with squamous cell carcinoma of the lung during treatment with nivolumab treatment [15].

In conclusion, the swing of pendulum from Hashimoto's to thyroid lymphoma and finally to GD as seen in our patient is relatively uncommon; clinicians need to continue screening for clinical and biochemical thyroid dysfunction in this subset of population who received R-CHOP therapy and preferably before even starting R-CHOP therapy. Additional long term

studies are needed to confirm the effect of chemotherapy on thyroid functions, especially R-CHOP therapy in patients with thyroid lymphoma.

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## Statement of Ethics

This manuscript has been cleared by the institutional review board. The patient has given written informed consent to publish the case (including publication of images).

## Disclosure Statement

The authors have no multiplicity of interest to disclose. We had published a case report pertaining to the initial presentation of our patient [16]. Different imaging cuts were used in this article.

Disclaimer: The views expressed in this article are those of the author and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government.

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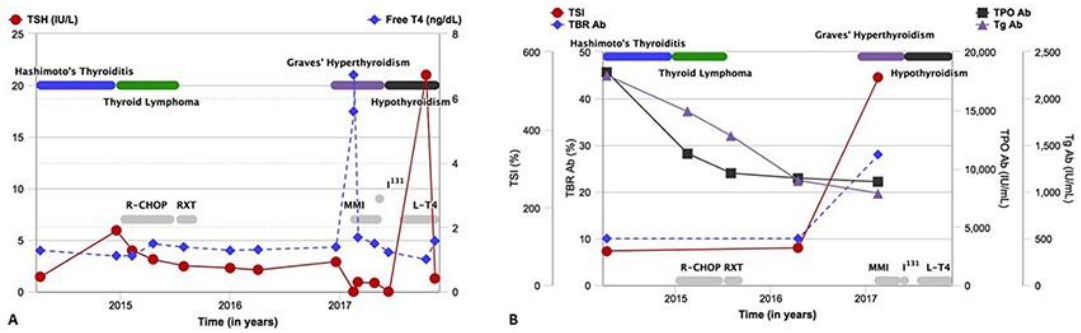


**Fig. 1.** **A** Course of the disease, from Hashimoto's thyroiditis (blue) to thyroid lymphoma (green) and then Graves' hyperthyroidism (purple). Hyperthyroidism was treated with methimazole/ $I^{131}$ and finally the patient developed hypothyroidism (brown) which was treated with levothyroxine. TSH (thyroid stimulating hormone, IU/L, shown in red color), and free T4 (free thyroxine, ng/dL, shown in blue color). **B** Course of the disease, from Hashimoto's thyroiditis (blue) to thyroid lymphoma (green) and then Graves' hyperthyroidism (purple). Hyperthyroidism was treated with methimazole/ $I^{131}$ and finally the patient developed hypothyroidism (brown) which was treated with levothyroxine. The X axis shows time (in years) and the Y axis shows the levels of thyroid antibodies: TSI (thyroid-stimulating immunoglobulin, shown in red color), TBRAb (thyroid receptor blocking antibody, blue color), TPO (thyroid peroxidase antibody, black color), TG Ab (thyroglobulin antibody, purple color).

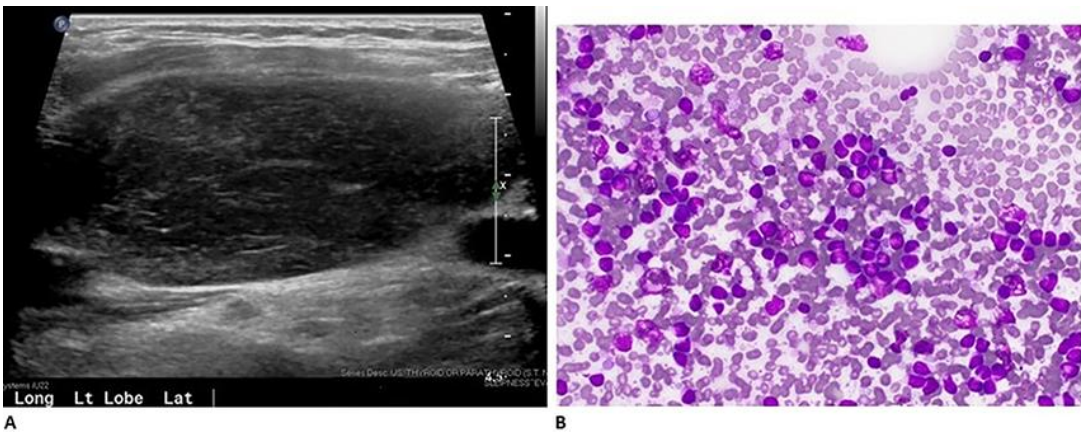


**Fig. 2.** **A** Thyroid ultrasound showing a dominant hypervascular left thyroid mass 5.9 × 2.7 × 4.4 cm. **B** Fine-needle aspiration biopsy of the left dominant thyroid nodule revealing background small lymphocytes, scattered plasma cells, and neutrophils with rare, large, atypical forms with prominent nucleoli (DiffQuik).

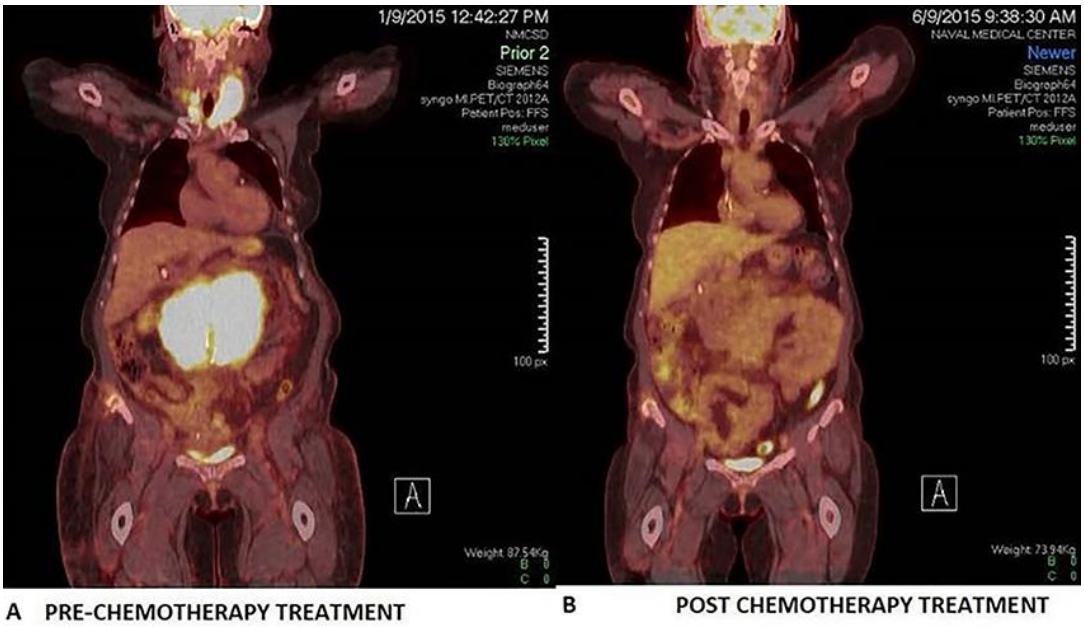


**Fig. 3.** **A** PET/CT of the chest and abdomen revealing a large retroperitoneal and mesenteric soft tissue mass, measuring 16 × 14 cm in greatest trans-axial dimension. The retroperitoneal mass encased the aorta and inferior vena cava as well as mesenteric vessels and both renal arteries. The mass also displaced the kidneys peripherally. **B** PET-CT scan showing resolution of fluorodeoxy-glucose (FDG) avid thyroid nodule and retroperitoneal mass.