

CASE REPORT

Oscillating hypothyroidism and hyperthyroidism – a case-based review

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Objective/Background: To discuss a unique clinical entity where inappropriate activity of inhibitory and stimulatory thyroid antibodies resulted in alternating hypothyroidism and hyperthyroidism.

Methods: We report the clinical history, laboratory data, and results of imaging studies, along with the pathophysiological mechanism and the subsequent treatment in a patient with fluctuating thyroid functional status.

Results: A 52-year-old female was treated for hypothyroidism for more than two decades. She started having symptoms of hyperthyroidism along with a suppressed thyroid-stimulating hormone (TSH). She continued to have persistent symptoms despite stopping her levothyroxine. Her free T3 and T4 were elevated along with an increased radioactive uptake scan. She was diagnosed with Graves' disease and started on methimazole, which relieved her symptoms for a few months. Subsequently, her TSH began to rise beyond expected level, her hypothyroid symptoms reappeared, and methimazole was discontinued. Following this, she again developed symptoms of hyperthyroidism and thyroid values revealed an undetectable TSH. She had at least two such documented cycles of hyperthyroidism alternating with hypothyroidism. She was eventually treated with radioactive iodine ablation followed by levothyroxine replacement. Swinging dominance of TSH-blocking autoantibodies (TBAb) and thyroid-stimulating autoantibodies (TSAb) triggered by methimazole and levothyroxine, respectively, is likely the underlying mechanism.

Conclusions: Physicians should be vigilant to the phenomenon of spontaneous conversion of hypothyroidism to hyperthyroidism, or vice versa, in a subset of patients with autoimmune thyroid disease. Repeated assessment of thyroid function along with measurement of TBAb and TSAb are invaluable in identifying this rare clinical entity.

Keywords: *hypothyroidism; hyperthyroidism; TBAb; TSAb; oscillating*

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Alternating hypo- and hyperthyroidism is a very rare, yet distinct, clinical entity in that the clinical presentation, molecular mechanism, and treatment strategy are unique from common thyroid disorders such as Graves' disease or Hashimoto thyroiditis. Here we report an immune-mediated case with two decades history of hypothyroidism that spontaneously developed hyperthyroidism, which was followed by oscillating thyroid function between hypo- and hyperthyroidism. We discuss recent developments of mechanistic insights and treatment options for this unique disorder.

Case report

A 52-year-old female with primary hypothyroidism for two decades was treated with levothyroxine 175 µg daily. Over a period of 2 years, her levothyroxine dose was

reduced to 25 µg daily because of persistently suppressed thyroid-stimulating hormone (TSH). She started to have typical symptoms of hyperthyroidism with palpitations, loose stools, insomnia, poor concentration, fatigue, cold intolerance, and weight loss over a period of 3 months. Her levothyroxine was therefore stopped but she remained symptomatic.

On physical examination, her vital signs were normal; she had intact memory, normal judgment and insight. She had lid lag and stare and a fine resting tremor. Her thyroid was palpable with no bruit or tenderness. The gland measured 30 g. Her TSH was 0.21 mIU/ml (normal 0.40–5.00) with a free thyroxine, T4 0.77 ng/dl (normal 0.71–1.85), and free triiodothyronine, T3 310 pg/ml (normal 230–420). Her radioactive iodine uptake scan revealed diffuse uptake of 54% (normal ≤ 35%) through

her enlarged thyroid gland. Her thyroid stimulating immunoglobulin (TSI) was elevated at 249% (normal <125%) and thyroglobulin was 263 ng/ml (normal 2.0–35). Her symptoms were consistent with Graves' disease and she was started on methimazole with prompt restoration of clinical euthyroidism and normalization of thyroid function for a few months.

Subsequently, her TSH began to rise beyond expected level, her hypothyroid symptoms reappeared, and methimazole was discontinued. Thyroid peroxidase antibody (TPOAb) was >1,000 IU/ml. She again developed symptoms of hyperthyroidism and thyroid values revealed an undetectable TSH. At this point, she was placed on propylthiouracil 25 mg daily. Four months later her TSH increased and her propylthiouracil was stopped. Her levothyroxine was restarted.

She had documented cycles of hypothyroidism alternating with hyperthyroidism. A complete evaluation of the hypothalamic-pituitary axis was done which was unremarkable.

She again started having symptoms of hyperthyroidism a third time after restarting levothyroxine and was finally treated with thyroid ablation with 12 mCi of radioactive iodine. Figure 1 depicts her fluctuating FT4 and TSH.

Discussion

There are two types of thyrotropin receptor (TSHR) autoantibodies found in immune disorders of the thyroid, namely thyroid-stimulating autoantibodies (TSAb) and TSH-blocking autoantibodies (TBAb). TSAb, by activating TSHR, is the direct cause of Graves' disease. In contrast, TBAb very rarely causes hypothyroidism by blocking endogenous TSH (1).

Takeda et al. (2) noticed that both types of TSHR antibodies can coexist in one patient, and the patient's thyroid function may change depending on the alteration in balance between these two types of antibodies. This will lead to a remarkable clinical phenomenon, where a patient can evolve from TBAb-induced hypothyroidism to TSAb-induced hyperthyroidism, or vice versa.

Recent studies on these two antibodies have additionally concluded that switching between TBAb and TSAb (or vice versa) occurs in rare patients after levothyroxine for hypothyroidism or anti-thyroid drug treatment for Graves' disease (3). These changes include differences in TSAb versus TBAb concentrations, affinities, and/or potencies. Namely, anti-thyroid drugs reduce initially low TSAb levels even further, leading to TBAb dominance; whereas, TSAb emergence after levothyroxine treatment may be sufficient to counteract TBAb inhibition, and trigger hyperthyroidism.

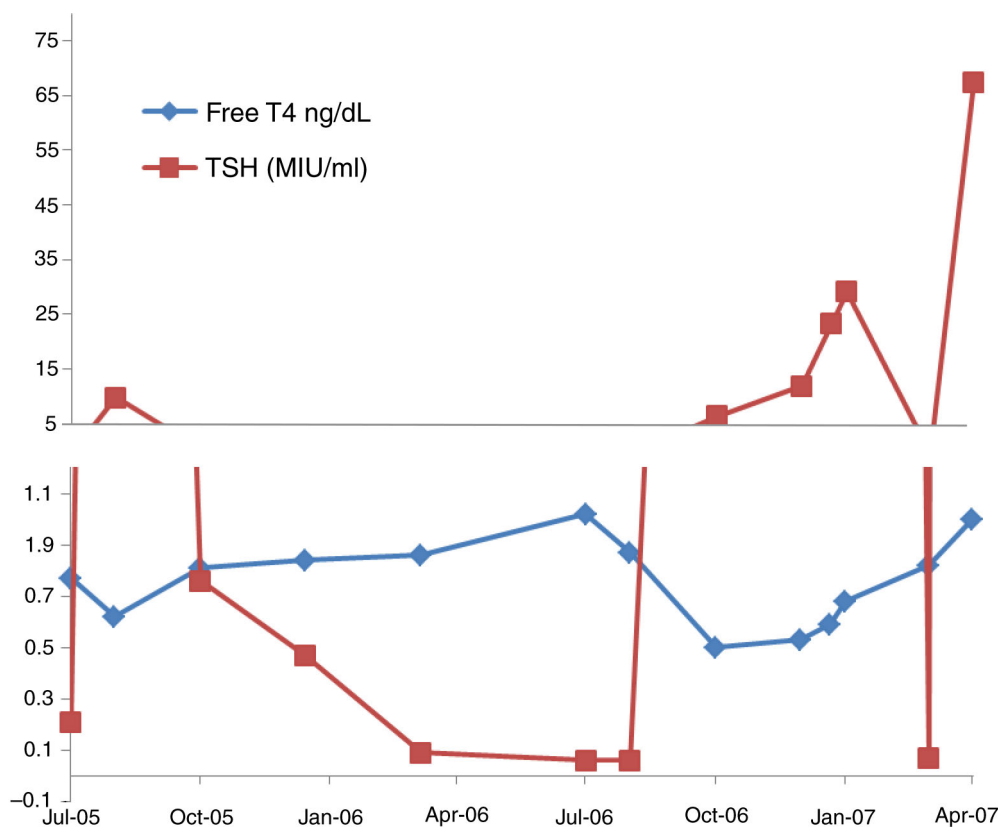


Fig. 1. Fluctuating free T4 and TSH values over time.

The patient in our case was diagnosed with hypothyroidism and achieved euthyroid status following treatment with levothyroxine. This quiescent status was disrupted two decades later when she developed hyperthyroidism. The etiology for her hypothyroidism was thought to be Hashimoto's thyroiditis (HT), which is usually an irreversible condition where massive lymphocytic infiltration and fibrosis destroy the hormone producing tissue, resulting in lifelong thyroid failure. An alternative explanation is that she had TBAb-induced hypothyroidism, which is distinct from HT, yet can have high TPOAb and thyroglobulin antibody (TgAb) (3). Important distinguishing clinical features of TBAb induced hypothyroidism as compared to HT includes thyroid atrophy presenting at onset of clinical disease. HT can have thyroid atrophy, but usually at advanced stage. Our patient's characteristic clinical course of oscillating thyroid function status in response to levothyroxine and methimazole/propylthiouracil is highly suggestive that she has underlying alternating TBAb and TSAb.

The occurrence of 'oscillating' emphasizes the need for careful patient monitoring and special management.

Adding levothyroxine along with methimazole could be an option, but close titration of individual drugs is essential to achieve euthyroidism, which requires frequent office visits and blood draws with added worries, expense, and inconvenience. Radioactive iodine (I-131) ablation followed by levothyroxine became the obvious choice to achieve a more permanent definitive solution. Of note, an alternating hypo- and hyperthyroidism are more commonly associated with ophthalmopathy (4). In patients with prominent eye symptoms, thyroidectomy may be considered given that radio-iodine is associated with worsening of ophthalmopathy. Management of children with autoimmune alternating hypo- and hyperthyroidism is challenging both from a medical and familial perspective.

I-131 ablation can be considered in older children (> 10 years). Younger children usually need surgery (5).

Conclusions

Physicians should be vigilant to the phenomenon of spontaneous conversion of hypothyroidism to hyperthyroidism, or vice versa, in a subset of patients with autoimmune thyroid disease. The thyroid function at the time of presentation should not be assumed as constant. Repeated assessment of thyroid function in patients with clinical symptoms of thyroid dysfunction along with measurement of TBAb and TSAb are invaluable in identifying this rare clinical entity of oscillating hypothyroidism and hyperthyroidism and initiating appropriate therapy.

Conflict of interest and funding

Authors declare no conflicts of interest.

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