Rhabdomyolysis in a Patient with Severe Hypothyroidism: A Case Report

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Case report

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Abstract

Background

Hashimoto's thyroiditis is typically diagnosed incidentally from elevated TSH or after evaluation of suggestive symptoms, including weight gain and fatigue. Rarely, patients present with an initial hyperthyroid state, Hashitoxicosis, that lasts weeks to months. Through a review of the current literature, it became apparent that this case is unique in several ways: the patient's age, lack of comorbid conditions, the unique presentation of her thyroid disease, as well as the development of acute kidney injury while hospitalized.

Case Presentation

Here we present the case of a 26-year-old female who was referred to the Endocrinology office in July 2019 with symptoms of hyperthyroidism. She has a positive family history of Graves' disease (GD) in her mother and thyroid malignancy in her maternal aunt. On her initial visit, TSH was suppressed, free thyroid hormones were increased, and both TPO and TSI antibodies were elevated. It was determined that this was likely a presentation of GD, and the patient was started on methimazole. She was instructed to follow-up every four weeks for monitoring of symptoms and labs. Three months following the initial visit, the patient failed to follow-up in office. During this time, she was seen by her primary care physician, diagnosed with hyperlipidemia, and started on statin therapy. One month later, on a subsequent follow-up with endocrinology, the patient complained of new onset back pain, muscle cramps, weight gain, and cold intolerance. She was sent to the emergency department for work-up. Evaluation revealed rhabdomyolysis in the setting of severe hypothyroidism, complicated by acute kidney injury. Her final diagnosis was found to be Hashitoxicosis with subsequent hypothyroidism.

Conclusions

Hyper- and hypothyroidism are two extremes on the spectrum of autoimmune thyroid disease, and the presentation can vary from patient-to-patient. Rarely, severe hypothyroidism can present with rhabdomyolysis with increased risk in patients on statin therapy. Thus, it is important to ensure patients are clinically and biochemically euthyroid prior to initiation of statin therapy. This case emphasizes the need for communication among physicians and the importance of patient adherence to treatment plans.

Introduction

Here we present the case of a 26-year-old Caucasian female diagnosed with thyrotoxicosis in April 2019. Thyrotoxicosis is the name for a range of clinical symptoms resulting from an excess of thyroid hormone, which can be elevated from a variety of pathologies. The most common cause of thyrotoxicosis is GD, making up 80% of thyrotoxicosis cases (1). The incidence of GD is highly influenced by genetics with approximately half those affected having a genetic predisposition (1). The symptoms of GD are widely known to include weight loss, palpitations, tremor, fatigue, exophthalmos, and possible development of a

palpable goiter. The diagnosis of GD involves evaluation of clinical signs and symptoms as well as laboratory tests for TSH, T4, or T3. In patients with GD, a typical biochemical picture of low TSH with elevated T3 and/or T4 is expected. Additional testing can be done for TSH receptor antibodies as well as a radioactive iodine uptake scan.

There are numerous other causes of thyrotoxicosis, including diffuse multinodular goiter, toxic adenoma, thyroid neoplasms, and thyroiditis. Thyroiditis causes a transient thyrotoxic state due to the release of preformed thyroid hormone from the thyroid gland. In the case of subacute, or De Quervain thyroiditis, there is an antigen related to a recent viral infection that causes activation of cytotoxic T cells. This leads to infiltration and inflammation of the thyroid gland. In addition to the release of preformed thyroid hormone, normal thyroid hormone production is also halted due to inflammation, leading to a subsequent hypothyroid state (1). Similar to subacute thyroiditis, painless thyroiditis is related autoimmune thyroid disease, has laboratory evidence of thyroid antibodies, and has a correlation with a family history of thyroid disorders. It can be self-limiting similar to subacute thyroiditis or, rarely, it can result in hypothyroidism (1).

Hashitoxicosis is the initial hyperthyroid state of Hashimoto's thyroiditis. In a mechanism similar to thyroiditis described above, the thyroid gland is destroyed through an inflammatory process, releasing preformed thyroid hormone (2). Due to this similar presentation to GD, it is crucial to differentiate the two disease processes. This can be done by radioiodine uptake scan in which one would expect diffusely increased uptake in the case of GD and diffusely decreased uptake in Hashimoto's thyroiditis (2). It can be difficult to differentiate these two pathologies using antibodies alone. In fact, greater than 99% of patients with Hashimoto thyroiditis and 74% of patients with GD both have elevated anti-thyroid peroxidase (anti-TPO) antibodies (3).

Case Report

The patient presented to the emergency department on April 30, 2019 with dizziness and lightheadedness associated with chest pain and shortness of breath. She was found to be hyperthyroid with a suppressed TSH. She was diagnosed with hyperthyroidism and started on beta blocker therapy. The patient presented to the Endocrinology office on July 31, 2019 for her initial appointment for management of thyrotoxicosis.

The patient has a past medical history of obesity and depression with no relevant surgical history. She has a family history of Grave's disease in her mother as well as thyroid malignancy in her maternal aunt. At the initial visit, her medications included metoprolol succinate, levonorgestrel implant, and paroxetine HCl. She is allergic to penicillin. The patient is a former smoker and denies a history of alcohol or drug abuse. At the initial appointment, the patient complained of heat intolerance, hot flashes, tremors, and palpitations of two months duration, and weight gain of 24 pounds in the previous 5 months. She also admitted to frequent, loose bowel movements and dry skin. Review of systems was further positive for shortness of breath, chest pain, and a rash in bilateral lower extremities. Review of systems was negative

for decreased energy, and she denied changes in her eyes, such as dryness, blurry vision, or redness. Physical exam was negative except for an enlarged, rubbery, nontender thyroid gland. Thyroid scan and uptake showed a low 24 hour uptake of 0.3%. Given the patient's family history, thyroid ultrasound findings, and persistence of thyrotoxicosis over several months, it was concluded that her clinical picture was suggestive of Grave's disease without ophthalmic involvement. The patient was started on methimazole 10 mg PO BID.

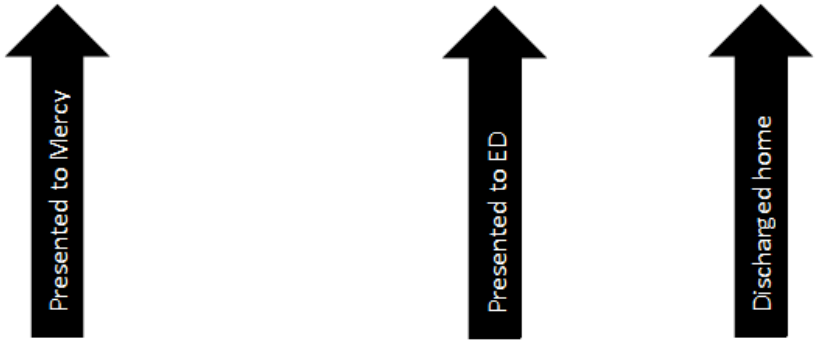
The patient followed up in the Endocrinology office on August 21, 2019. On this date, she reported significant improvement in her symptoms, including heat intolerance, hot flashes, and tremors. Her methimazole dose was decreased to 5 mg daily, and she was started on Vitamin D3 2,000 units daily. Following this visit, the patient lost to follow-up. The patient was seen by her primary care provider at an outside facility where she was diagnosed with hyperlipidemia. She was prescribed Rosuvastatin 20 mg daily. She reestablished care at the Endocrinology office on October 21, 2019 with new onset low back pain and a 30 pound weight gain since the last visit. Additionally, she complained of new onset cold intolerance, extreme fatigue, muscle cramps, and constipation. Lab results revealed markedly elevated TSH, undetectable free T4, and significantly elevated CK (See Table 1). The patient was advised to come to the emergency department for further evaluation.

The patient was diagnosed with rhabdomyolysis in the setting of severe primary hypothyroidism. During her 3 day hospital stay, Rosuvastatin was discontinued, and the patient was started on levothyroxine 75 mcg IV daily. Her hospital stay was complicated by acute kidney injury, but the patient was discharged home upon improvement of labs on day 3. The patient was discharged on levothyroxine 100 mcg daily. During outpatient follow-up 2 weeks later, the patient reported improved cold intolerance, hot flashes, and constipation. She continued to experience muscle cramps, dysphagia to solids and liquids, and fatigue. The levothyroxine dose was increased to 150 mcg daily based on persistently elevated TSH (See Table 1). The patient followed up in the endocrinology office again on December 5, 2019. Her metoprolol succinate dose was held due to resolution of symptoms. At the next visit on January 16, 2020, she reported improvement in hot flashes and bowel movements. Labs from this day showed elevated LDL cholesterol, elevated TPO and TSI antibodies, with TSH and thyroid hormones within normal limits. (See Table 1). Of note, TPO antibodies were persistently greater than 900 IU/mL while TSI antibodies were trending down at 1.8 IU/mL (slightly above upper range of normal), confirming the diagnosis of Hashitoxicosis with subsequent hypothyroidism.

Discussion

Table 1

	4/2019	7/31	8/20	10/21	10/21	10/24	11/6	12/4	1/16
TSH	0.01	<0.01	0.03	131.70	-	-	93.03	3.41	1.26
Free T4	3.2	3.94	0.60	<0.02	-	-	0.90	1.67	1.59
Free T3	-	376	1.9	0.4	-	-	2.0	3.3	3.3
TSI Ab	-	1.7	-	2.6	-	-	-	-	1.8
TPO Ab	-	>900	-	-	-	-	-	-	>900
Vit D	-	19	-	17	-	-	-	30	-
Creatinine	-	-	-	1.53	1.51	1.21	0.99	0.78	0.72
GFR	-	-	-	41	42	54	>60	>60	>60
CK	-	-	-	1,506	1,198	968	428	141	-



There are several mechanisms thought to explain hyperlipidemia during a hypothyroid state. First, thyroid hormone increases 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase activity in the liver. Second, thyroid hormone increases the expression of LDL receptors on fibroblasts and in the liver. Third, thyroid hormone increases levels of HDL cholesterol as well as hepatic lipase activity (4). In the absence of pathology, each of these mechanisms work to decrease cholesterol. In patients with uncontrolled hypothyroidism, a lack of thyroid hormone inhibits these processes and raises cholesterol levels. Furthermore, TSH and lipid levels have a linear relationship. Meaning, as TSH levels increase, LDL, total cholesterol, and triglycerides increase as well (5).

The first line treatment for hyperlipidemia is statin therapy, which works by inhibiting HMG-CoA reductase. While myalgia is a well-documented side effect of statin therapy, rhabdomyolysis is considered to be rare complication. From November 1997 through March 2000, the FDA Adverse Event Reporting System database shows 601 cases of statin-associated rhabdomyolysis (6). The risk of developing rhabdomyolysis with statin use is increased with elevated concentrations of the drug. This can occur with impaired drug metabolism or changes in the volume of distribution, which are based on age, sex, body size, renal and hepatic function in addition to conditions like diabetes and hypothyroidism (6). Furthermore, other medications can increase or decrease the activity of cytochrome P-450 3A4 enzymes, which are responsible for metabolism of statin drugs. 55% of reported rhabdomyolysis cases mentioned previously were in patients taking prescription medications that affect the metabolism of statins, including fibrates, cyclosporine, macrolide antibiotics, warfarin, digoxin, and azole antifungal medications (6).

Several possible mechanisms for stain-induced muscle injury have been proposed. First, reducing cholesterol levels also reduces the cholesterol content in cell membranes of skeletal muscle, increasing fragility (6). Second, studies have shown that patients on statin therapy have low serum coenzyme Q levels, which may adversely affect oxidative phosphorylation in muscular tissue. Additionally, in one study, muscle biopsy of patients treated with statins showed an increased lactate to pyruvate ratio, reflecting impaired aerobic metabolism at the level of the mitochondria (6). Interestingly, a third theory describes a dose-dependent increase in apoptosis of smooth muscle cells for atorvastatin, lovastatin, and simvastatin. This theory may explain how statins decrease cardiovascular risk. If a similar pattern were occurring in skeletal muscle cells, it could explain the muscle damage sometimes seen with status use (6).

Our patient's course was complicated by acute kidney injury. It is theorized that hypothyroidism itself affects renal function by decreasing cardiac output and increasing systemic and renal vasoconstriction, which reduces renal blood flow and glomerular filtration rate (GFR) (7). One study found that GFR significantly decreased with increased TSH levels in patients with high-normal TSH values. More specifically, a correlation was found between TSH values and renal impairment at TSH levels beginning at 2.5-3.0 μIU/mL (8). In addition to hypothyroidism alone, rhabdomyolysis also contributes to renal injury. This is thought to be due to myoglobin, a protein released by muscles during breakdown. Myoglobin affects renal vasoconstriction, forms intratubular casts, and is toxic to kidney cells (9).

Interestingly, our patient had both elevated thyroid stimulating immunoglobulin (TSI) and anti-TPO antibodies. Hashimoto's thyroiditis and GD exist on a spectrum of autoimmune thyroiditis. Rarely, we can see overlapping disease processes at certain points in the timeline of disease (2). A few cases have been reported in the medical literature in which the same patient presented with either extreme of the autoimmune thyroid spectrum. The exact mechanism of the variable presentation remains unknown, but it is thought to be related to fluctuating levels of stimulatory and inhibitory thyroid antibodies (10). Another explanation would be long-standing autoimmune inflammation, resulting in hypothyroidism, but we believe this is less likely in the case of our patient.

Through a review of the current literature, it became apparent that this case is unique in several ways: the patient's age, lack of comorbid conditions, the unique presentation of her thyroid disease, as well as the development of acute kidney injury while hospitalized. There are only a handful of other cases that report on acute kidney injury in the setting of rhabdomyolysis induced by statin use and hypothyroidism. Additionally, most cases of statin-induced rhabdomyolysis are precipitated by exercise. As described earlier, the risk of developing rhabdomyolysis is increased with age, preexisting conditions, and other prescription medications (6). At 26 years old, our patient was very young compared to other cases and lacked other serious health conditions.

From our experience with this case, we recommend that all patients undergo thyroid laboratory evaluation prior to starting statin therapy. The American Thyroid Association Guidelines for Detection of Thyroid Dysfunction recommends that adults be screened for thyroid dysfunction via serum TSH beginning at the

age of 35, repeated every 5 years (11). Conversely, in 2015 the U.S. Preventative Services Task Force published guidelines recommending against regular thyroid screening due to insufficient evidence (12). We also recognize the limitations of electronic medical records (EMR) in this clinical scenario. One possible remedy to this problem would be a universal EMR to better facilitate patient care between primary care providers and specialists. Creating a policy requiring a note to primary care providers with any medication changes could also aid in physician-to-physician communication. Lastly, this case demonstrates that patient education is vital. Patients must be counseled on the importance of follow-up lab tests, especially in the case of drugs with a narrow therapeutic index, such as levothyroxine. Additionally, patient education when starting a statin should include a warning to stop the medication with any unexplained muscle fatigue or soreness.

Abbreviations

GD – Graves Disease

Anti-TPO - anti-thyroid peroxidase

Anti-Tg - anti-thyroglobulin

HGM-CoA - 3-hydroxy-3-methyl-glutaryl-CoA

GFR – glomerular filtration rate

TSI - thyroid stimulating immunoglobulin

EMR – electronic medical records

Declarations

Ethics approval and consent to participate

This case report was exempt from Mercy Hospital's IRB process because it meets the following criteria: 2 or less patients involved AND no identifiable information included.

Consent for publication

Consent for the writing and publication of this case report was obtained from the patient.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NG analyzed and interpreted the patient data. MW wrote the manuscript. NG edited and approved the final manuscript.

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Not applicable.

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