An Atypical Presentation of Apathetic Thyrotoxicosis Requiring Thyroidectomy In The Acute Setting

Matthew Koh, BS
West Virginia University, School of Medicine, Morgantown, WV

Melissa LoPinto, MD, MPH, FACS
Department of Surgery, West Virginia University, Morgantown, WV

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Corresponding Author: Matthew Koh, BS, West Virginia University School of Medicine, One Medical Center Drive, Morgantown, WV 26505. Email: mokoh@mix.wvu.edu

Abstract

Apathetic thyrotoxicosis is an atypical manifestation of thyrotoxicosis characterized by depression, lethargy, and weakness. Patients are often elderly and have no known history of hyperthyroidism. Typical symptoms of hyperthyroidism such as hyperkinetic motor activity and exophthalmos are often absent. In the classical description, apathetic thyrotoxicosis is a distinct clinical entity, however the end stage presentation of typical thyrotoxicosis may result in apathy with considerable overlap in clinical features. This unique case illustrates a scenario in which untreated typical thyrotoxicosis progressed to an apathetic state, thus suggesting that apathetic thyrotoxicosis and end stage untreated thyrotoxicosis may be variations of the same disease process rather than distinct clinical entities. Here we present a 53 year old woman with typical Graves’ disease, treated initially with methimazole. She developed methimazole-induced agranulocytosis, requiring cessation of treatment. After a period of inadequate treatment, she re-presented in a clinically apathetic state, with biochemically uncontrolled hyperthyroidism. Following emergent medical stabilization, she successfully underwent definitive total thyroidectomy.

Case Presentation

A 53 year old Caucasian woman presented to her local physician with symptomatic hyperthyroidism and exophthalmos. She was diagnosed with Graves’ disease and was prescribed methimazole, but developed agranulocytosis. The methimazole was discontinued and she was treated with metoprolol only. Previous ophthalmology exam documented thyroid eye disease including dry eyes, mild inflammation, sensation of pressure with headache, horizontal diplopia, proptosis and lid lag. Due to ocular manifestations and concomitant tobacco use, she was not considered a candidate for radioactive iodine ablation. The methimazole was discontinued and she was treated with metoprolol only. Previous ophthalmology exam documented thyroid eye disease including dry eyes, mild inflammation, sensation of pressure with headache, horizontal diplopia, proptosis and lid lag. Due to ocular manifestations and concomitant tobacco use, she was not considered a candidate for radioactive iodine ablation. For unclear reasons, she did not have a surgical consultation at that time. Several months later, she presented at her local emergency room with a 2-day history of nausea and vomiting, a 1-month history of tachycardia with palpitations, and anxiety. She reported losing approximately 30 pounds over the previous several months. On arrival at our tertiary care facility, she was cachectic, tachycardic, lethargic and experienced difficulty concentrating and swallowing. She appeared catatonic. She had been taking extended release metoprolol 50mg daily as prescribed, with no history to suggest overdose. She was not able to give a history. She could only concentrate long enough to answer brief “yes and no” questions. Despite having no focal neurologic deficits, she was generally weak, especially her swallowing and respiratory mechanisms. She was unable to safely pass a swallow evaluation. Her breathing was weak and she required bipap support. She had tachycardia to 150 bpm and atrial fibrillation. Laboratory evaluation revealed elevated thyroid function (TSH of <0.003, free T4 of 3.28, free T3 of 6.0), and thrombocytopenia (platelet count 104,000 decreasing to 68,000 on repeat evaluation). Additional laboratory values shown in Table 1. 

Due to her history of methimazole-induced agranulocytosis, thioamide drugs were contraindicated. Thus, she was started on Lugol’s solution (potassium iodide) and hydrocortisone. For cardiac stabilization, she was managed with esmolol and cardizem drips. To avoid Jod-Basedow phenomenon with prolonged administration of Lugol’s solution, she was scheduled for definitive total thyroidectomy. Preoperative platelet transfusion corrected her thrombocytopenia. On day 4 of Lugol’s solution
treatment, she underwent an uneventful total thyroidectomy. Postoperatively, she was monitored in the intensive care unit. By postoperative day three, her mental status had returned to baseline. She was able to swallow safely, tolerate oral nutrition, and converse appropriately. Pathology revealed a 24.5g goiter demonstrating multinodular hyperplasia.

**Discussion**

Agranulocytosis is a rare complication of thioamide treatment, resulting in decreased amounts of neutrophils, eosinophils, basophils, and mast cells. Thrombocytopenia is a separate immune mediated manifestation of thyrotoxicosis. Agranulocytosis is estimated to occur in 0.2-0.5% of patients with Graves’ disease receiving thioamide treatment. It is more likely to occur in older and in female patients. Onset of agranulocytosis is acute and typically can cause fever and sore throat, but can also be asymptomatic. Diagnosis is typically established by an absolute neutrophil count (ANC) of < 500/μL. It is hypothesized that neutrophils oxidize thioamide drugs into reactive metabolites, which induces an immune response and eventual death of neutrophils. Treatment of thioamide-induced agranulocytosis involves immediate cessation of thioamide treatment and initiation of IV broad-spectrum antibiotics, followed by definitive thyroid treatment. In this case, cessation of methimazole was implemented, however her hyperthyroidism was not managed definitively. Beta-blocker only therapy is insufficient as it fails to treat the underlying hyperthyroidism and may delay definite treatment by masking symptoms. This patient was not considered a candidate for radioactive iodine ablation due to her ocular manifestations and tobacco use. It is unclear why she was not referred for surgical management at the time of diagnosis.

After a period of inadequate treatment, she re-presented with apathetic thyrotoxicosis and subsequently underwent definitive total thyroidectomy. Apathetic thyrotoxicosis is associated with depression, apathy, weight loss, and tachycardia. It is not associated with typical symptoms of Graves’ disease, such as exophthalmos and hyperkinetic motor activity. Although apathetic thyrotoxicosis can occur at any age, it is typically encountered in elderly patients. The absence of typical symptoms may cause the diagnosis to be elusive. Subclinical hyperthyroidism may go unrecognized and untreated, eventually resulting in apathetic thyrotoxicosis. Despite the classic description of apathetic thyrotoxicosis, variable presentations have been reported in the literature. Previously reported series and cases are summarized in Table 2.

The exact pathogenic mechanism behind development of apathetic thyrotoxicosis is unclear. One theory suggests that the amount of catecholamines in the brain is

### Table 1. Laboratory Data on Arrival to Tertiary Care Facility

| LAB           | VALUE     | REFERENCE RANGE |
|---------------|-----------|-----------------|
| WBC           | 7.4 x 10^3/uL | 3.5-11 x 10^3/uL |
| HEMOGLOBIN    | 9.8 g/dL   | 11.2-15.2 g/dL  |
| HEMATOCRIT    | 30.6%      | 33.5-45.2%      |
| PLATELET COUNT| 104 x 10^3 | 140-450 x 10^3  |
| SODIUM        | 140 mmol/L | 136-145 mmol/L  |
| POTASSIUM     | 4.9 mmol/L | 3.5-5.1 mmol/L  |
| BICARB        | 19 mmol/L  | 22-32 mmol/L    |
| CHLORIDE      | 110 mmol/L | 96-111 mmol/L   |
| BUN           | 35 mg/dL   | 8-25 mg/dL      |
| CREATININE    | 0.54 mg/dL | 0.49-1.1 mg/dL  |
| GLUCOSE       | 58 mg/dL   | 65-139 mg/dL    |
| CALCIUM       | 8.3 mg/dL  | 8.5-10.4 mg/dL  |
| PHOSPHORUS    | 4.2 mg/dL  | 2.4-4.7 mg/dL   |
| MAGNESIUM     | 2.2 mg/dL  | 1.6-2.5 mg/dL   |
| BILIRUBIN TOTAL| 0.9 mg/dL | 0.3-1.3 mg/dL |
| BILIRUBIN DIRECT | 0.3 mg/dL | <0.3 mg/dL |
| AST           | 67 U/L     | 8-41 U/L        |
| ALT           | 12 U/L     | <55 U/L         |
| ALKALINE PHOSPHATASE | 145 U/L | <150 U/L         |
| LDH           | 484 U/L    | 125-220 U/L     |
| TROPOIN       | 12 ng/L    | 0-30 ng/L       |
| BNP           | 100 pg/ml  | <=100 pg/ml     |
decreased. Another theory posits that the catecholamine receptor becomes unresponsive. This case demonstrates a potential link between the untreated hyperthyroid state and the progression to the apathetic state. While this patient is atypically young and did manifest exophthalmos, her disease was untreated much in the way a subclinical patient may not be treated. The untreated hyperthyroid state may result in physiologic unresponsiveness or physiologic “burn out”, leading to the apathetic state. This unusual case demonstrates a history consistent with typical thyrotoxicosis but an acute presentation with features of apathetic thyrotoxicosis suggesting that apathetic thyrotoxicosis may be a variation of end stage thyrotoxicosis rather than a truly distinct entity. Moreover, this case illustrates the unique situation where carefully planned total thyroidectomy in the acute setting is necessary for optimal and definitive management.

### Conclusion

Agranulocytosis is a rare complication of thioamide treatment. Awareness, monitoring, and recognition are critical to appropriate management, which includes immediate cessation of thioamide treatment. Once medications are stopped, definitive management should be initiated with either radioactive iodine ablation or surgery. Given the need for timely intervention, early surgical referral should be initiated as soon as the diagnosis of agranulocytosis is made. This is especially true in patients who are not optimal candidates for radioactive iodine ablation. Such cases would include toxic multinodular goiter or those with significant exophthalmos and tobacco use. Early surgical intervention would have prevented progression of this patient's disease. Her progression manifested as atypical apathetic thyrotoxicosis.

In the acute setting, apathetic thyrotoxicosis, like typical presentations of thyrotoxicosis, must be managed urgently. Management includes thioamide medications and inorganic potassium iodide to treat the underlying disease; steroids to calm autoimmune thyroiditis; beta-blockers and calcium channel blockers for cardiac stabilization and symptom relief. Surgery should not be undertaken emergently due to increased risk of perioperative thyroid storm. Once medical management is initiated, carefully planned, definitive total thyroidectomy in the acute setting may be necessary for optimal and definitive management.

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