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Case Report

A Rare Case of Thyrotoxic Periodic Paralysis in a Patient With Concomitant Methimazole-Induced Agranulocytosis

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ABSTRACT

Background/Objective: Thyrotoxic periodic paralysis (TPP) is a rare condition causing weakness of the lower extremities associated with significant hypokalemia. Likewise, agranulocytosis due to methimazole use is a rare occurrence. We present the first documented case of concomitant TPP and agranulocytosis from methimazole use.

Case Report: A 48-year-old woman presented with sore throat, fevers, odynophagia, and sudden-onset bilateral leg weakness. Methimazole had been started 10 weeks prior for a new diagnosis of Graves' disease. On admission, the patient was febrile, tachycardic, thyrotoxic, and neutropenic. She also experienced near-paralysis of the lower extremities. She was diagnosed with TPP and treated with beta blockade. She was admitted to the intensive care unit and started on broad-spectrum antibiotics, lithium, and propranolol for treatment of septic shock and hyperthyroidism, respectively. Given persistent hypokalemia despite 2 days of therapy, she was also diagnosed with refeeding syndrome.

Discussion: TPP is a rare entity, though it should be considered on the differential for any thyrotoxic patient presenting with sudden weakness. If the associated hypokalemia does not begin to normalize within 48 h of beta blockade, other etiologies should be investigated. Lastly, alternative treatments such as lithium may be used to control hyperthyroidism in patients with methimazole-induced agranulocytosis.

Conclusion: While methimazole-induced agranulocytosis and thyrotoxic periodic paralysis are independently rare diagnoses, the combination of the 2 is exceedingly rare, and our case represents the first documented case in the literature reflecting a patient suffering from both syndromes.

Introduction

Thyrotoxic periodic paralysis (TPP) is a rare syndrome causing weakness of the lower extremities associated with significant hypokalemia.[1] TPP can often be confused with other types of acute hypotonic paralysis as it is not often encountered in clinical practice, with incidence ranging from 0.1% to 0.2% of thyrotoxic patients in the North American population[2] to 1.8% to 1.9% of thyrotoxic patients in Asian populations.[3,4] Diagnosis is often established with a finding of hypokalemia during an acute attack of lower extremity weakness in the setting of thyrotoxic state. Likewise, agranulocytosis due to methimazole use is also a rare occurrence, with an incidence around 0.1% to 0.8%.[5,6] Diagnosis can be made if there is temporal correlation with use of offending medication and other etiologies ruled out.[7] We present the first documented case of concomitant TPP and agranulocytosis from methimazole use.

Abbreviations: °C, degrees in Celsius; ALT, alanine transaminase; ANA, antinuclear antibody; ANC, absolute neutrophil count; anti-RNP, anti-ribonucleoprotein; anti-SSA, anti-Sjögren's-syndrome-related antigen A; anti-SSB, anti-Sjögren's-syndrome-related antigen B; anti-TPO, anti-thyroid peroxidase; AST, aspartate transaminase; BMP, basic metabolic panel; BUN, blood urea nitrogen; CBC, complete blood count; g/dL, grams per deciliter; h, hour; IU/L, international units per liter; IU/mL, international units per milliliter; K/cumm, thousands per cubic millimeter; mcg/dL, micrograms per deciliter; MCV, mean corpuscular volume; mEq, milliequivalents; mg, milligram; mg/dL, milligrams per deciliter; min, minutes; mmHg, millimeters of mercury; mmol/L, millimoles per liter; ng/dL, nanograms per deciliter; ref, reference; T4, thyroxine; TPP, thyrotoxic periodic paralysis; TRAb, thyrotropin receptor antibody; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; U/L, units per liter; uIU/mL, micro-international units per milliliter; WBC, white blood cell.

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Case Report

A 48-year-old Hispanic woman with a past medical history of recently diagnosed Graves' disease initially presented with sore throat, fevers, and odynophagia for 4 days. Two days before she came to the emergency department, she had ingested several servings of pasta and subsequently started experiencing rapid-onset leg weakness preventing her from walking. Her recent medical history included a diagnosis of Graves' disease made 10 weeks prior, at which time she was started on methimazole 20 mg daily. Family history was negative for any thyroid disease or autoimmune conditions. On admission, the patient's temperature was 38.2 °C, heart rate 140 beats per minute, blood pressure 85/50 mmHg, respiratory rate 20/min, and oxygen saturation 94% on room air. On exam, patient was alert and oriented. Thyroid exam was remarkable for a symmetrical goiter 3 times the upper limit of normal with smooth texture. Examination of the oropharynx was significant for thrush. The patient had 4 out of 5 strength in the bilateral upper extremities and 2 out of 5 strength in the bilateral lower extremities. She reported no prior history of significant weakness.

Her laboratory tests were remarkable for a white blood cell count and absolute neutrophil count that were both undetectable (Table). Potassium was low at 2.6 (ref: 3.5-5.1 mmol/L), and phosphorus was low at 1.4 (ref: 2.5-4.5 mg/dL). Her thyroid function tests were consistent with hyperthyroidism with TSH <0.01 (ref: 0.27-4.2 uIU/mL) and free T4 4.04 (ref: 0.93-1.7 ng/dL). Prior to admission, anti-TPO was >600 (ref: ≤ 34.0 IU/mL), TRAb was 22.0 (ref: ≤ 2.0 IU/L), and TSI was 287% baseline (ref: <140%). When agranulocytosis was noted, additional history was obtained. The patient had never received chemotherapy, radiotherapy, or immunotherapy nor had a known underlying hematological disease.

Table
Lab Tests

Lab test	Result
CBC	
WBC	<0.5 K/cumm (4.5-10)
ANC	<0.5 K/cumm (1.8-8.0)
Hemoglobin	12.5 g/dL (12.0-14.6)
Hematocrit	36.7% (36.0-44.0)
Platelets	92 K/cumm (160-360)
Bands	<10% (0-9)
MCV	72.3 fL (82.0-97.0)
BMP	
Sodium	124 mmol/L (135-145)
Potassium	2.6 mmol/L (3.5-5.1)
Chloride	86 mmol/L (100-110)
Bicarbonate	23 mmol/L (20-30)
BUN	12 mg/dL (7-18)
Creatinine	0.46 mg/dL (0.50-1.0)
Glucose	337 mg/dL (65-99)
Phosphorus	1.4 mg/dL (2.5-4.5)
Liver Panel	
Protein	6.3 g/dL (6.0-8.0)
Albumin	3 g/dL (3.5-5.0)
Total bilirubin	1.4 mg/dL (<1.0)
Direct bilirubin	1 mg/dL (<0.3)
Alkaline phosphatase	108 U/L (35-104)
AST	24 U/L (10-35)
ALT	16 U/L (10-35)
Miscellaneous	
TSH	<0.01 uIU/mL (0.27-4.20)
Free T4	4.04 ng/dL (0.93-1.70)
Lactate	4.1 mmol/L (0.5-2.2)
Cortisol	57.9 mcg/dL (4.8-19.5)
Procalcitonin	14.6 ng/mL (<0.25)
Aldolase	8.2 U/L (<8.1)
Creatinine kinase	101 U/L (20-180)

Highlights

- TPP should be considered for any thyrotoxic patient presenting with acute weakness.
- Gentle potassium repletion is recommended to prevent rebound hyperkalemia.
- Methimazole-induced agranulocytosis may require alternative treatments such as lithium.

Clinical Relevance

While methimazole-induced agranulocytosis and thyrotoxic periodic paralysis are rare diagnoses on their own, the combination of the 2 is exceedingly rare, and our case represents the first documented case in the literature reflecting a patient suffering from both syndromes.

The patient was admitted to the intensive care unit and started on vancomycin, cefepime, fluconazole, and vasopressors. Blood cultures obtained on admission were positive for methicillin-sensitive *Staphylococcus aureus*, and computed tomography imaging of the thorax demonstrated likely right lung pneumonia. Ultrasound of the thyroid showed heterogenous and hypervascular gland. The patient received a preliminary clinical diagnosis of TPP and was treated with low-dose potassium repletion and propranolol. Neurology was consulted and recommended broad work-up for lower extremity weakness, which included negative results for acetylcholine receptor binding antibody, striated muscle antibody, aldolase, creatinine kinase, ANA, anti-SSA, anti-SSB, anti-smooth muscle antibody, anti-RNP antibody, and vitamin deficiencies. Magnetic resonance imaging of the spine and computed tomography head did not reveal any acute findings contributing to her sudden weakness. She received lithium 300 mg orally every 8 h, levocarnitine 1,000 mg liquid orally every 12 h, propranolol 10-20 mg orally every 8 h, and dexamethasone 2 mg intravenously every 8 h for treatment of her thyrotoxicosis. Several doses of filgrastim were administered with subsequent resolution of neutropenia. Given mild improvement in weakness and electrolyte abnormalities including hypokalemia and hypophosphatemia after 2 days of therapy, concomitant re-feeding syndrome was also suspected (though the patient did not experience a significantly decreased oral intake prior to hospital presentation), so potassium was repleted more frequently. Within 2 days of propranolol administration, the potassium increased from 2.6 (ref: 3.5-5.1 mmol/L) on admission to 3.5 mmol/L. Three days after initiation of therapy, the repeat TSH remained <0.01 (ref: 0.27-4.2 uIU/mL), and the repeat free T4 decreased from 4.04 to 1.72 (ref: 0.93-1.7 ng/dL). However, after 2 weeks of hospitalization, the patient still experienced persistent hyperthyroidism refractory to medical management with free T4 increasing to 3.33, so patient underwent a total thyroidectomy complicated by transient postoperative hypocalcemia. Final pathology showed multinodular goiter. After surgery, antithyroid treatment was discontinued, and weight-based levothyroxine was started. Potassium at time of discharge was 4.0-4.5 mmol/L. At her 1-month endocrinology follow-up

appointment, she was well-appearing with improvement of her lower extremity weakness.

Discussion

Thyrotoxic periodic paralysis is a rare syndrome and can often be confused with other types of acute hypotonic paralyses, as it is not often encountered in clinical practice.[3,4] TPP most often presents in the 20–40-year-old age group, though cases outside the range have been documented, with a higher incidence in males.[1,8,9] Diagnosis is often established with a finding of hypokalemia during an acute attack of weakness with preserved consciousness in the setting of thyrotoxic state. TPP is known to affect the proximal muscles more than the distal muscles as well as the legs more than the arms,[1] with complaint of mild myalgia present in a minority of patients.[8] Our patient had greater lower extremity weakness as compared to upper extremity weakness and had a concomitant complaint of myalgia of her bilateral lower extremities similar to other reported cases. Typically, weakness resolves around several hours but can extend to days[8]; our patient's weakness took days to improve, likely due to the acute onset of TPP compounded by concomitant refeeding syndrome and persistent hypokalemia requiring more aggressive potassium repletion than typical for isolated TPP. TPP attacks can be precipitated by high-insulin or epinephrine states which can increase the movement of potassium out of the bloodstream and into the cells, thereby decreasing the serum levels of potassium.[8] Thus, stress, ingesting a high-carbohydrate load, or rest after physical activity can all precipitate TPP.[9] Our patient ingested a large carbohydrate-heavy meal of pasta hours prior to onset of her paralysis.

In terms of biochemical characteristics of TPP, the mean level of serum potassium in 1 study was 2.1 mmol/L.[10] On admission, our patient's potassium was 2.6 mmol/L. Treatment of TPP involves low-dose repletion of potassium, which may also lead to improvement of the patient's weakness. Rebound hyperkalemia can occur in approximately 40% of cases,[11,12] as there is not typically a total body depletion of potassium, but rather a transient influx of potassium into the cells during TPP. Treatment with beta-blockade results in potassium release from the cells back into the bloodstream and thus recovery from the paralysis. In light of this phenomenon, some studies suggest slower potassium repletion rates (<10 mEq/hr) given the risk of rebound hyperkalemia.[1,12] For our patient, potassium was initially repleted at 40 mEq per day given the high likelihood of rebound hyperkalemia as documented above. Since low-dose repletion plus beta blockade in our patient led to minimal improvement of the potassium levels, the primary team adopted a more aggressive repletion approach. To ensure another reversible cause was not being missed, an extensive work-up for the patient's weakness was conducted which was unremarkable. Thus, the constellation of hypokalemia and sudden-onset acute weakness in a thyrotoxic patient with a known trigger largely confirms the diagnosis of TPP.

Agranulocytosis due to methimazole use is also a rare occurrence. Since our patient was still thyrotoxic when the methimazole was discontinued, dexamethasone, levo-carnitine, and lithium were initiated as alternative treatments. Lithium has been shown by multiple small-scale studies to be an effective alternative regimen for patients intolerant to thionamides or who experience adverse effects such as liver enzyme abnormalities and agranulocytosis.[13,14] Lithium plays a role in inhibiting the synthesis and release of thyroid hormone.[15] Levocarnitine is a peripheral antagonist of thyroid hormone action inhibiting both T3 and T4 entry into cell nuclei, and in 1 double-blind, randomized placebo-controlled clinical trial, was found to be effective in reversing and preventing symptoms of hyperthyroidism with an added benefit of bone mineralization.[16,17] At our institution, severe hyperthyroidism and thyroid storm are treated with levocarnitine as there is no toxicity, teratogenicity, or known interaction between levocarnitine and other medications or conditions. Plasmapheresis was not used, as it was not available at our institution. Newer immunomodulatory agents are also being developed for the treatment of Graves' hyperthyroidism, including rituximab,[18] though none have entered mainstream clinical practice at this point. Often thyroidectomy is the definitive therapy for patients with TPP. Prior case reports have described the phenomenon of recurrent TPP attacks that resolved with total thyroidectomy.[19]

Finally, another rarity in this presentation relates to the patient's demographics, most notably in her being a middle-aged Hispanic female, whereas patients with TPP are more likely to be Asian, male, and in their 20-30s.

Conclusion

While methimazole-induced agranulocytosis and thyrotoxic periodic paralysis are rare diagnoses on their own, the combination of the 2 is exceedingly rare, and our case represents the first documented in the literature reflecting a patient suffering from both syndromes. This case provides several learning points relating to patient care. First, TPP is a rare hyperthyroidism-related hypokalemia caused by a rapid intracellular shift of potassium that can result in weakening of the extremities; therefore, TPP should be on the differential for any thyrotoxic patient presenting with sudden weakness. Second, to prevent rebound hyperkalemia, potassium should be gently repleted. However, patients who have both an intracellular shift of potassium from TPP as well as a total body loss of potassium from refeeding syndrome may require more aggressive potassium repletion. Lastly, alternative treatments such as lithium may be used to control hyperthyroidism in patients with methimazole-induced agranulocytosis.

Disclosure

The authors have no conflicts of interest to disclose.

Acknowledgment

Patient consent was obtained prior to the submission of this case report.

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