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| RESEARCH ARTICLE

Life Saving Cure, Harmful Turn: PTU-Induced Neutropenia in a Patient with Thyroid Storm

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| ABSTRACT

Though it stands as the first line and life-saving therapeutic option in thyroid storms, Propylthiouracil (PTU) remains a double-edged sword, fraught with rare yet potentially life-threatening adverse effects. This case report underscores PTU-induced neutropenia in a 34-year-old Saudi female with a two-year history of Grave's disease. Having ceased antithyroid medications on her own accord and being in the third month postpartum, these factors together served as sufficient catalysts to precipitate a severely symptomatic thyrotoxic crisis. The patient was managed with supportive care, hydrocortisone, propranolol, and PTU; yet on the fourth day following admission to the intensive care unit, her neutrophil count plummeted precipitously, indicating severe PTU-induced neutropenia, thereby rendering PTU permanently contraindicated. This case report illustrates that management of thyroid storm remains achievable without PTU; however, definitive treatment ultimately necessitates thyroidectomy, particularly when radioactive iodine is contraindicated, as was the case here owing to the postpartum state.

| KEYWORDS

Thyrotoxicosis, Thyrotoxic crisis, Thyroid storm, Hyperthyroidism, Antithyroid medications, Propylthiouracil, Agranulocytosis, Neutropenia, Hyperthermia.

| ARTICLE INFORMATION

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1. Introduction

Thyroid storm, also known as thyrotoxic crisis, is an acute, life-threatening complication of hyperthyroidism that is characterized by multi-organ dysfunction [1]. It can be described as an exaggerated presentation of thyrotoxicosis where patients develop an intense hypermetabolic state induced by excessive release of thyroid hormones with high fever, profound tachycardia (often >140 bpm), arrhythmias, cardiac failure, and marked central nervous system disturbances (e.g., agitation, delirium, seizures, or coma), along with gastrointestinal/hepatic dysfunction (e.g, nausea, vomiting, abdominal pain, jaundice) [1,2]. This life-threatening complication is most observed when an individual with underlying hyperthyroidism, particularly Graves' disease, is subjected to a stressor. Common stressors include infections, trauma or surgery, diabetic ketoacidosis, myocardial infarctions,

parturition or pregnancy complications, and abrupt withdrawal of antithyroid therapy. Iodine exposure (e.g. contrast studies or amiodarone) and thyroidectomy also frequently precipitate storm [1,3]. Unrecognized or untreated thyroid storm rapidly progresses to multi-organ failure; historically the untreated mortality approaches 90% [2]. Even with modern intensive care, the in-hospital mortality remains high, often cited as roughly 10–25% [1,3]. Fatality in thyroid storm usually results from cardiac arrhythmia, congestive heart failure, severe hyperthermia, and multi-organ failure [1]. According to epidemiological research papers, thyroid storm is rare, with an incidence reported of 0.2–0.8 cases per 100,000 population per year, roughly 1–2% of hospitalized hyperthyroidism cases [3]. It is more common in women and in older patients, who also tend to fare worse [3]. A recent population-based analysis found that while younger patients <60 years of age have relatively low storm mortality estimated around 1–2%. The 30-day death rate in older patients (>60 years) rises steeply up to 10–17% [3]. These data underscore that thyroid storm is a medical emergency. The consequences of neglecting storm treatment are fatal, as it can lead to a cascade of severe complications and outcomes, such as cardiac arrest, hepatic failure, coma, and shock. Hence, prompt and aggressive treatment is a necessity [1,2]. The approach to managing thyroid storm is based on four fundamental principles: (1) rigorous and intensive supportive measures, including temperature control by cooling, intravenous fluids, oxygen supplementation, and ICU-level observation; (2) blockage and inhibition of the synthesis and release of thyroid hormones; (3) prevention of peripheral thyroid hormone effects; and (4) identification and management of any possible underlying or triggering cause. In clinical practice, this is applied by initiating high-dose antithyroid drugs like thionamides, beta-adrenergic blockade, inorganic iodine, which should be given only after thionamide, and glucocorticoids, often simultaneously [1]. For instance, IV propranolol is administered to bring down the heart rate and mitigate adrenergic symptoms [1]. A thionamide like propylthiouracil or methimazole is administered at a high loading dose, often 500–1000 mg of PTU, then 250 mg q4–6h, or methimazole 20 mg q4–6h, to block new thyroid hormone synthesis [1]. Potassium iodide or Lugol's solution is administered about an hour later to acutely block hormone release from the gland [1]. High-dose glucocorticoids (e.g. hydrocortisone 100 mg IV q8h) serve a dual role: they inhibit peripheral conversion of T4 to the more active T3 and may address relative adrenal insufficiency [1,4]. Supportive measures like cooling blankets, antipyretics, IV glucose, and definitive treatment of any infection or other trigger are also essential in improving overall prognosis [1,4]. A well-established fact is that both propylthiouracil (PTU) and methimazole are effective antithyroid medications, but they differ in pharmacodynamics. PTU has the extra ability of blocking the peripheral deiodination of T4 to T3, a capability that methimazole lacks; this has historically made PTU the drug of choice in thyroid storms [1,4]. In the acute setting, PTU can lower circulating T3 levels more rapidly, up to a 45% drop at 24 hours, compared to methimazole, which achieves the rate of approximately 10–15% at 24 hours [5]. In contrast, methimazole has a longer half-life and achieves euthyroidism more quickly over days to weeks, with less risk of severe hepatotoxicity [4,5]. Most guidelines, though, including the 2016 American Thyroid Association recommendations, suggest using PTU as first-line therapy in thyroid storm, largely for its peripheral T3-blocking effect and rapid action [1,6]. Notably, recent observational studies have questioned whether outcomes differ significantly between PTU and methimazole in storms, but PTU remains entrenched in acute management protocols [6,7]. Like all medications, PTU has a well-defined adverse-effect profile. Common side effects include rash, arthralgias, and mild gastrointestinal upset, while serious complications—though rare—can be life-threatening. Notably, PTU carries a boxed warning for severe hepatotoxicity and acute liver failure [4]. Immune-mediated vasculitis syndromes like ANCA-positive glomerulonephritis have also been reported [4]. Of relevance in this case, PTU and methimazole both can cause agranulocytosis, a profound neutropenia that predisposes to severe and fatal infections [4]. This idiosyncratic reaction occurs in roughly 0.2–0.5% of patients taking PTU, most often within the first few months of therapy [4,5]. Its mechanism is not fully understood; hypothesized causes include drug metabolism by neutrophil myeloperoxidase leading to toxic metabolites, as well as immune-mediated destruction of granulocytes and drug-dependent anti-neutrophil antibodies [5]. In reported series, PTU-induced agranulocytosis typically affects middle-aged adults (often women) [5] and can be fatal if unrecognized. Management requires immediate discontinuation of the offending drug and supportive care (e.g. broad-spectrum antibiotics and hematopoietic growth factors) while an alternative hyperthyroidism therapy is instituted [5]. The present case is unusual and instructive because it combines two rare events: a thyroid storm and PTU-induced neutropenia. Simultaneous occurrence of thyrotoxicosis and agranulocytosis is extremely rare; there are very limited cases reported in literature that described thyroid storm complicated by antithyroid drug–induced agranulocytosis [8]. This overlap poses a treatment dilemma and a clinical conundrum, where the indispensable drug that saves lives also risks provoking a life-threatening hematologic crisis. It is critical and mandatory to spread awareness and recognize this complication early because ongoing PTU therapy will worsen neutropenia, while switching to methimazole is contraindicated by cross-reactivity. For the mentioned reasons, this case report emphasizes the necessity of careful monitoring of blood counts upon PTU initiation and the need to consider alternative methods such as iodine, steroids, plasmapheresis, or surgery as salvage therapies to manage the patient's condition when usual treatments fail or cause harm. We present this case to illustrate the diagnostic and management challenges posed when a "life-saving cure" unexpectedly induces a severe toxicity and to emphasize lessons for clinical practice.

2. Case Presentation

2.1 Patient's history and Physical Examination

This case report outlines a 34-year-old Saudi female, who is married, has three children, does not smoke, and has been known to have Grave's disease for the past two years, with poor compliance to treatment. Her Grave's disease was diagnosed at the age of 30 and was previously managed with carbimazole, which she discontinued a few months ago on her own due to concerns about weight gain. Her family history was noncontributory, except for the fact that her mother suffers from hypothyroidism. She was brought to our emergency department by her family due to increasing confusion and severe anxiety over the preceding few hours. Her symptoms initially began with palpitations, subjective fever, diarrhea, and tremors, which rapidly progressed to sweating, restlessness, and agitation. The patient explicitly denied any contact with sick individuals, recent life stressors, recurrent infections, recent iodine exposure, alcohol consumption, or drug use. While she complained of fast, irregular palpitations at presentation, she did not report any cough, shortness of breath, or chest pain. Notably, she was in her third month postpartum. On physical examination, she was found to be tachycardic with a heart rate of 158 bpm (irregular pulse), hypertensive at 150/80 mmHg, tachypneic with a respiratory rate of 26/min, and maintaining an SpO_2 of 95% on room air. She appeared agitated and sweaty, with a diffuse goiter. Examination of the chest, cardiovascular system, and abdomen were unremarkable. No edema or skin rash was noted in her extremities, although palmar erythema was observed by the physicians. Bedside ECG revealed atrial fibrillation with rapid ventricular response (RVR).

2.2 Investigations

With thyroid storm secondary to Grave's disease, triggered by the combination of postpartum stress and antithyroid medication withdrawal, the following laboratory workup was performed (Table 1).

Test	Result	Normal Range
Hemoglobin	12	12-16 g\dL
WBC	5.5	4.0-11x10^9\L
Platelets	220	150-450x10^9\L
TSH	<0.01	0.4-4.0 mIU\L
Free T4	60	10-22 pmol\L
Free T3	22	3.5-6.5 pmol\L
Sodium	132	135-145 mmol\L
Potassium	4.2	3.5-5.0 mmol\L
ALT	76	<40 U\L
AST	60	<40 U\L

Table 1: results of relevant investigations.

2.3 Management course

Immediate stabilization in the emergency department was prioritized, with plans underway to transfer the patient to the intensive care unit for close monitoring. Given concerns regarding her ability to maintain the airway, initial treatments were administered intravenously. Intravenous fluids, paracetamol, propranolol, hydrocortisone, and Propylthiouracil (PTU) 200 mg every 4 hours via nasogastric tube were all given. After one hour, 5 drops of Lugol's iodine via nasogastric tube were scheduled to be administered every 8 hours. By the fourth day, the patient showed initial improvement—her agitation was settling, and her heart rate had decreased to 110 bpm. Yet, she began to complain of a severe sore throat and malaise. Repeat laboratory tests revealed a white blood cell count of 0.9×10^9/L and an absolute neutrophil count of 250 cells/μL, indicating severe neutropenia/agranulocytosis. PTU was immediately discontinued, and broad-spectrum intravenous antibiotics—specifically piperacillin-tazobactam—were initiated, while hydrocortisone, iodine, and propranolol were continued. A full septic workup was also conducted to screen for potential sepsis. PTU was considered permanently contraindicated, and an urgent total thyroidectomy was planned as the definitive treatment, as radioiodine was avoided due to its delayed onset of action and the patient's recent postpartum status. As anticipated, the neutrophil count recovered following the cessation of PTU, and after careful preoperative preparation, the patient underwent a successful curative thyroidectomy.

3. Discussion

Though hormonal levels of T4 and T3 might be extremely high in some cases, they do not always reflect how severe the disease is, making thyroid storm primarily a clinical diagnosis rather than a laboratory one [1]. Some patients with mild derangements can still experience life-threatening storms [2]. Therefore, physicians should consistently consider using a scale like the Burch-Wartofsky Point Scale (BWPS) or the Japan Thyroid Association (JTA) criteria for a more accurate assessment [2]. For instance, a BWPS score >45 strongly suggests thyroid storm, with points assigned for involvement of the CNS, liver, gastrointestinal system, presence of hyperthermia, and identification of a possible trigger [2]. Given the mortality rate of 10–30% for thyrotoxic crisis managed in hospitals, empiric treatment should never be delayed for the sake of laboratory confirmation [3]. While most cases

of thyroid storms have an identifiable trigger, a subset presents without any clear cause [1,2]. In this case, it is reasonable to assume that her trigger was postpartum stress combined with antithyroid medication withdrawal, underscoring the critical importance of medication compliance in preventing thyroid storm [3]. Although postpartum thyroiditis is typically mild and self-limiting, it must be considered in the differential; however, her history of Grave's disease provided sufficient evidence to rule it out [7]. Had that not been the case, progression to hypothyroidism followed by spontaneous recovery would have supported the diagnosis of postpartum thyroiditis [7]. Due to its rapid onset of action, most clinical guidelines recommend PTU as the initial therapy in thyroid storm [4,5]. Nonetheless, because of its well-documented hepatotoxicity, it should be transitioned to methimazole once the patient stabilizes, as PTU is not advisable for long-term use [5,7]. Although agranulocytosis occurs in only about 0.2–0.5% of cases, it remains one of the most serious complications associated with propylthiouracil [5]. PTU-induced neutropenia typically emerges within the first three months of initiation, yet it can still present abruptly and without warning, as illustrated in this case [5]. While classic signs include sore throat, malaise, and fever, it is well-documented that PTU-induced neutropenia may develop silently, without any clinical manifestations [5]. To prevent mortality from sepsis, early detection is paramount. Multiple studies have shown that immediate cessation of PTU combined with the early administration of broad-spectrum antibiotics can be lifesaving in such scenarios [4]. In situations where PTU leads to severe adverse effects during life-threatening thyroid storm, alternative and non-standard treatment options must be considered [9]. The literature has discussed several such alternatives, including cholestyramine to interrupt enterohepatic recirculation of thyroid hormones, lithium therapy, or plasmapheresis in particularly critical cases. Still, these approaches serve only as a temporary bridge toward definitive management, which remains surgical intervention [9]. While radioactive iodine could have been a viable definitive option, its use is limited by both its delayed mechanism of action and its contraindication during the postpartum period [7,9]. Several case series have shown that some patients with thyroid storm can be successfully managed with iodine, beta blockers, and steroids alone—without the use of PTU—yet true resolution continues to rely on thyroidectomy [7].

4. Conclusion

Thyroid storm is a purely clinical diagnosis, as the hormonal levels of T4 and T3 bear no consistent correlation with the severity of the condition. Life-threatening thyroid storms may yet lurk behind mild laboratory derangements, thus compelling physicians not to delay empiric treatment in pursuit of laboratory confirmation. While PTU remains the first-line, life-saving agent in cases of thyroid storm, it is nevertheless a double-edged sword, owing to its rare but potentially fatal complication of agranulocytosis. Once recognized, PTU-induced neutropenia demands the immediate discontinuation of PTU and close monitoring of the complete blood count. This further underscores the importance of patient education regarding the potential side effects of antithyroid medications. Ultimately, the management of thyroid storm without PTU remains possible; yet true medical wisdom lies in preparedness—in anticipating complications before they arise.

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