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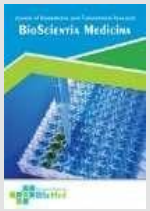

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Destructive Thyroiditis: A Rare and Perplexing Complication of Lithium Therapy in Bipolar Disorder

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A B S T R A C T

Background: Lithium is a cornerstone therapy for Bipolar I Disorder, yet its use necessitates vigilant monitoring for adverse drug reactions (ADRs). While lithium-induced hypothyroidism is a well-documented complication, the emergence of thyrotoxicosis secondary to destructive thyroiditis is a rare and diagnostically challenging event. This report presents a systematic analysis of a case of suspected lithium-induced thyroiditis notable for its paradoxical clinical presentation as a severe depressive episode. **Case presentation:** A 33-year-old female with a 10-year history of Bipolar I Disorder, stable on lithium for two years, was admitted with a severe depressive episode and active suicidal ideation. The onset of her psychiatric decompensation was temporally correlated with a diagnosis of thyrotoxicosis (suppressed TSH <0.005 uIU/mL; elevated FT4 >7.77 ng/dL). A formal causality assessment using the Naranjo Adverse Drug Reaction Probability Scale yielded a score of 6, indicating a "probable" relationship between lithium and the thyroiditis. Critically, the thyrotoxic state, which conventionally mimics mania, presented atypically as severe depression. **Conclusion:** This case of probable lithium-induced destructive thyroiditis, presenting paradoxically with severe depression, underscores the critical need for a high index of suspicion for iatrogenic endocrinopathies in patients on lithium who exhibit any mood destabilization. A systematic approach to ADR assessment is essential to guide appropriate clinical management in such complex presentations.

1. Introduction

Pharmacovigilance, the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem, is a critical component of modern clinical practice.[1] Case reports of rare or atypical adverse drug reactions (ADRs) serve as the foundation of post-marketing surveillance, generating signals that can inform clinical guidelines and enhance patient safety. Lithium, a cornerstone in the long-term management of Bipolar I Disorder, is a medication with a well-established efficacy but also a significant ADR signal potential due to its narrow therapeutic index and multi-system effects.[2] Its use mandates vigilant monitoring, particularly for endocrine, renal, and neurological complications.

The thyroid gland is a primary target for lithium's adverse effects, as it actively concentrates the ion to levels significantly higher than in the serum.[3] This accumulation is known to interfere with multiple stages of thyroid hormone synthesis and release, most commonly resulting in goiter and hypothyroidism. The proposed mechanisms for lithium-induced hypothyroidism are multifaceted, including the inhibition of thyroid-stimulating hormone (TSH)-stimulated adenylate cyclase and the reduction of iodine uptake and organification.[4] In contrast, the development of hyperthyroidism, particularly

thyrotoxicosis resulting from a non-autoimmune, destructive thyroiditis, is a much rarer and less understood complication.[5] Destructive thyroiditis involves a direct cytotoxic effect on thyroid follicular cells, leading to an unregulated release of preformed hormones and a state of thyrotoxicosis.[6] This presents a profound diagnostic challenge in patients with bipolar disorder due to the significant phenomenological overlap between the neuropsychiatric symptoms of thyrotoxicosis (irritability, anxiety, psychomotor agitation, insomnia, tachypsychia) and the core features of a manic or hypomanic episode.[7] This clinical mimicry can lead to the misattribution of symptoms to a psychiatric relapse, potentially resulting in the catastrophic clinical decision to increase the dose of lithium, thereby exacerbating the underlying iatrogenic pathology.[8]

The scientific contribution and novelty of this report are centered upon the systematic analysis of a highly atypical and paradoxical clinical presentation of this rare ADR.[9] In a stark departure from the established literature, the patient in this case developed a severe and progressively worsening depressive episode that was temporally correlated with the onset of her thyrotoxic state. The existence of "apathetic hyperthyroidism," a variant characterized by depressive features, is recognized but remains a rare clinical entity. This case, therefore, provides a valuable addition to the sparse literature on atypical, depressive presentations of lithium-induced thyrotoxicosis.[10] This report has three primary aims. First, to systematically analyze a case of suspected lithium-induced thyroiditis with a paradoxical depressive presentation in accordance with the CARE (Case Report) guidelines. Second, to formally assess the causality of the drug-event relationship using a validated ADR probability scale. Finally, to explore the potential pathophysiological and neurobiological mechanisms that may underlie this paradoxical response and to discuss the complex, evidence-based clinical decision-making process required in its management.

2. Case Presentation

The patient was a 33-year-old, unmarried female with a Bachelor's degree in literature, employed as a professional model and restaurant manager. She self-presented to the Emergency Department of Ari Canti Hospital on March 1st, 2025. The primary impetus for her presentation was a constellation of severe depressive symptoms that had been present for approximately five months and had reached a critical intensity in the preceding month. The patient's chief complaints included pervasive sadness, severe insomnia, significant anergia, anorexia, and the emergence of active suicidal ideation. The acuity of her condition was underscored by an aborted self-harm attempt on the morning of admission, which prompted her to seek immediate psychiatric intervention. A summary of the patient's demographic and presenting information is provided in Figure 1. The information presented in Figure 1 establishes the foundational clinical context of the case, highlighting the patient's high-functioning baseline and the severity of her acute depressive presentation, which she directly linked to her recent medical diagnosis.

The patient’s severe depressive episode had an insidious onset approximately five months prior to her admission, in October 2024. The emergence of these psychiatric symptoms was temporally correlated with the onset of a new constellation of physical symptoms, which included palpitations, a visible swelling in her neck (goiter), significant unintentional weight loss from a baseline of 60 kg, and a notable proptosis of her eyes (exophthalmos). Following a referral to an internist, a diagnostic workup confirmed a diagnosis of thyroiditis, and she was commenced on treatment with thiamazole and propranolol. Despite the initiation of treatment for her endocrine condition, her mood continued to deteriorate, ultimately culminating in the need for psychiatric hospitalization. This depressive presentation was in stark contrast to her state approximately one year prior, which she described in terms consistent with a hypomanic or manic episode. During that period, she reported experiencing boundless energy, a significantly

decreased need for sleep, and engagement in impulsive and high-risk behaviors, such as excessive shopping and reckless driving. A detailed timeline of these events is presented in Figure 2. As detailed in Figure 2, the timeline clearly illustrates the critical temporal relationship between the onset of the patient's iatrogenic thyroid disease and the emergence of her severe depressive episode, a key feature of this case.

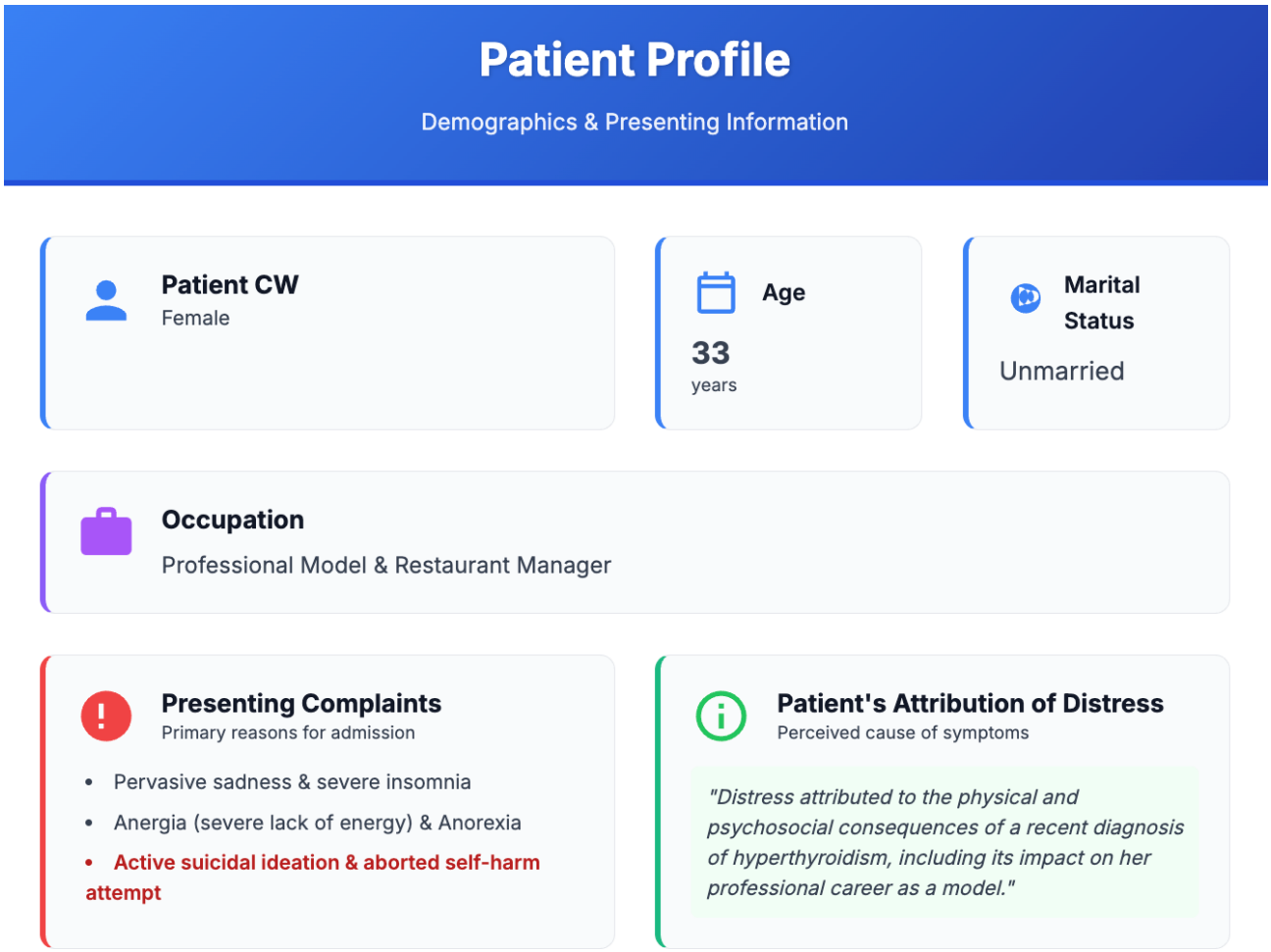

Figure 1. Patient profile: Demographics & presenting information.

The patient had a well-established, 10-year history of Bipolar I Disorder, with her initial diagnosis occurring at the age of 23. Her illness had been characterized by a recurrent course of both depressive and manic episodes. Her treatment history was complex, involving consultations with several different psychiatrists and a period of inconsistent medication adherence. However, for the two years immediately preceding this admission, she had achieved a period of sustained euthymia on a maintenance regimen of lithium 200 mg twice daily and quetiapine 200 mg at bedtime. Her family history was positive for bipolar disorder in her mother, who was reportedly untreated. Her past medical history was significant only for the recently diagnosed thyroiditis. Her complete pharmacological regimen on admission is detailed in

Figure 3. The information in Figure 3 provides a comprehensive overview of the patient's longitudinal history, highlighting the chronicity of her psychiatric illness, her recent period of stability on lithium, and the specific medications implicated in her current presentation.

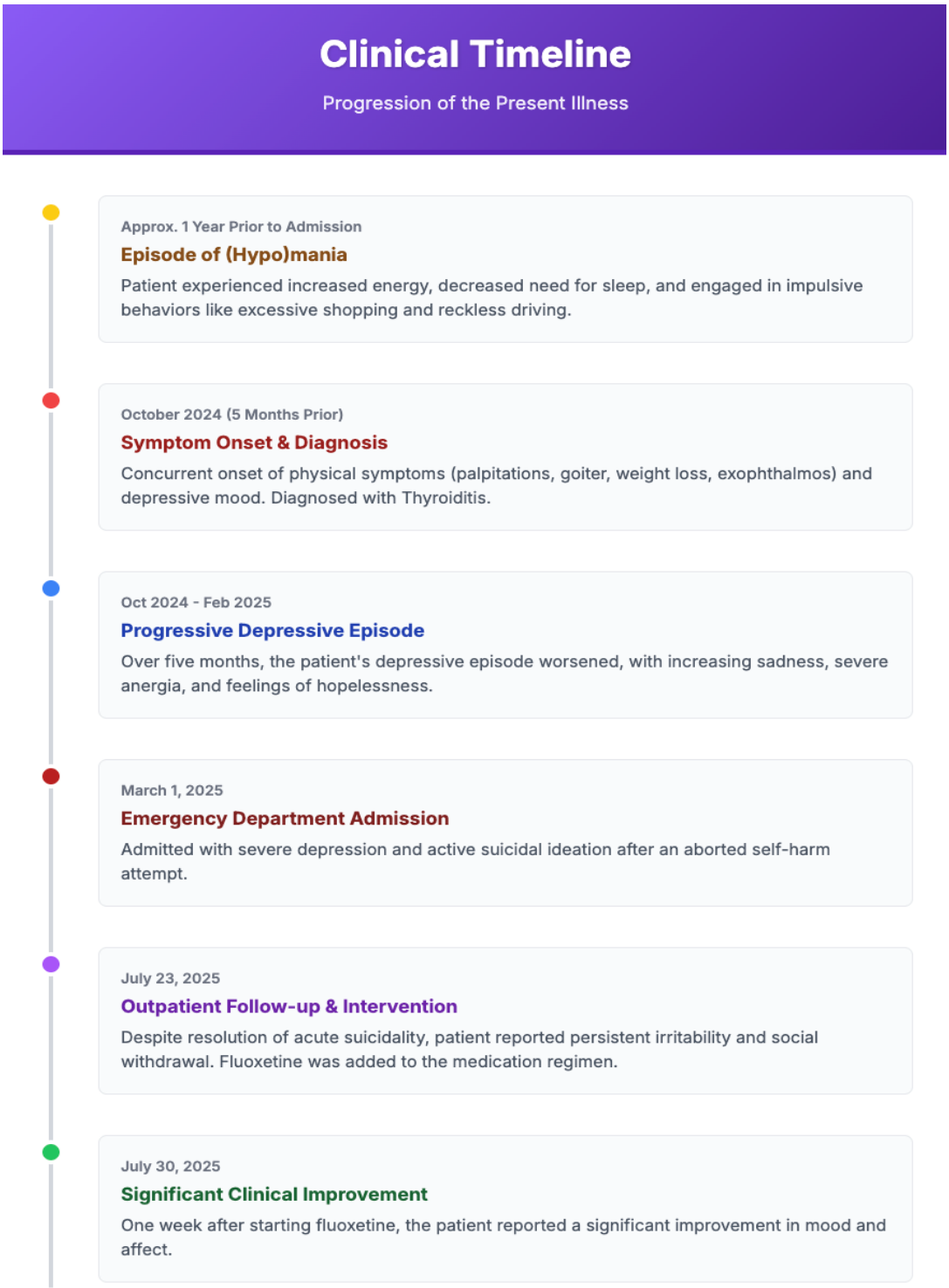

Figure 2. Timeline and features of the present illness.

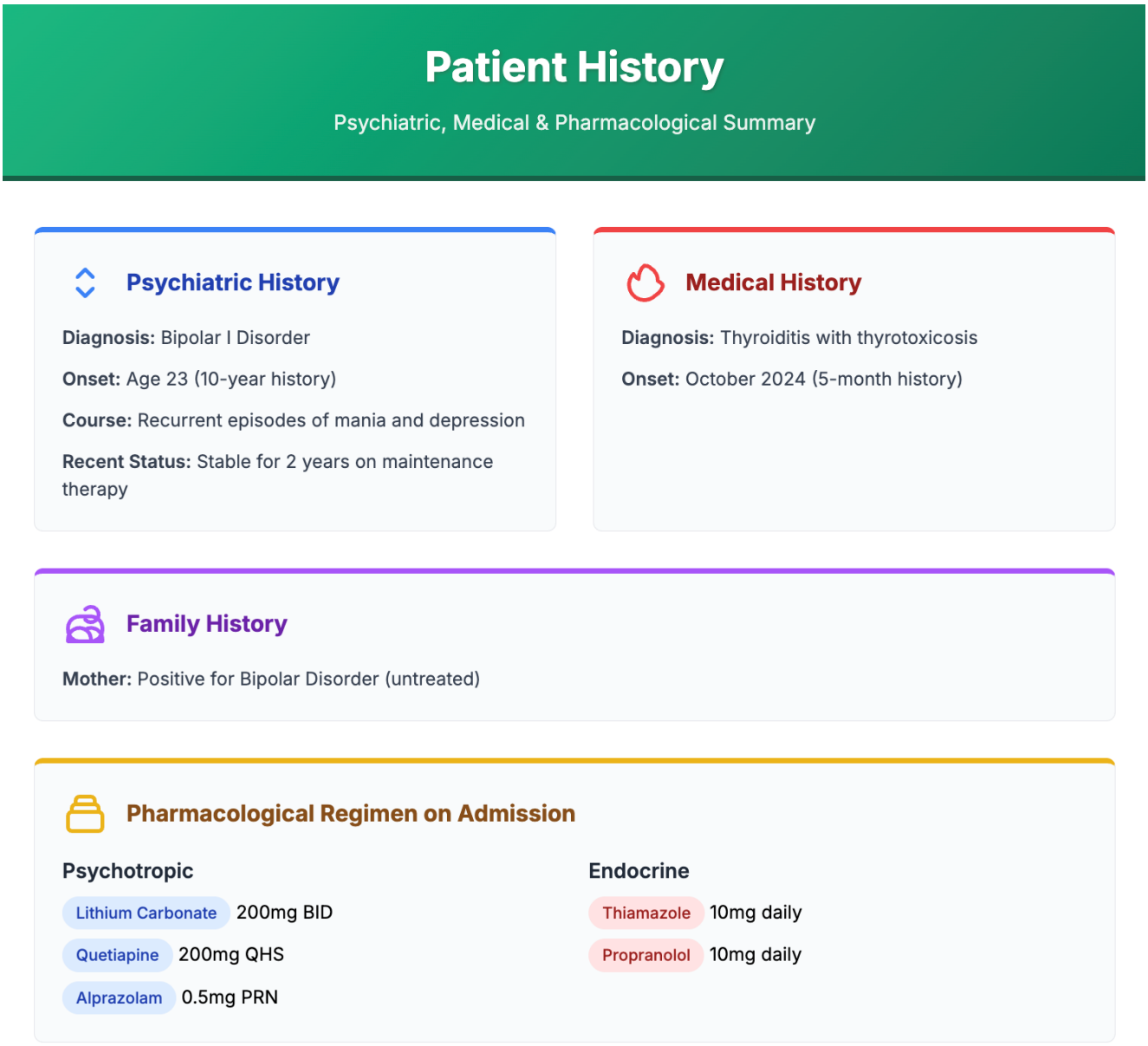

Figure 3. Past psychiatric, medical, and pharmacological history.

Upon examination in the Emergency Department, the patient's vital signs and anthropometric measurements were largely within normal limits, with the exception of a pulse rate at the upper end of the normal range. The physical examination was unremarkable, apart from the known exophthalmos. The neurological examination was non-focal, with the patient being fully conscious, alert, and oriented. A summary of the key findings is provided in Figure 4. The findings in Figure 4 are significant in that they largely exclude an acute medical or neurological crisis as the primary cause of her altered mental state, thus pointing towards her known psychiatric and endocrine conditions.

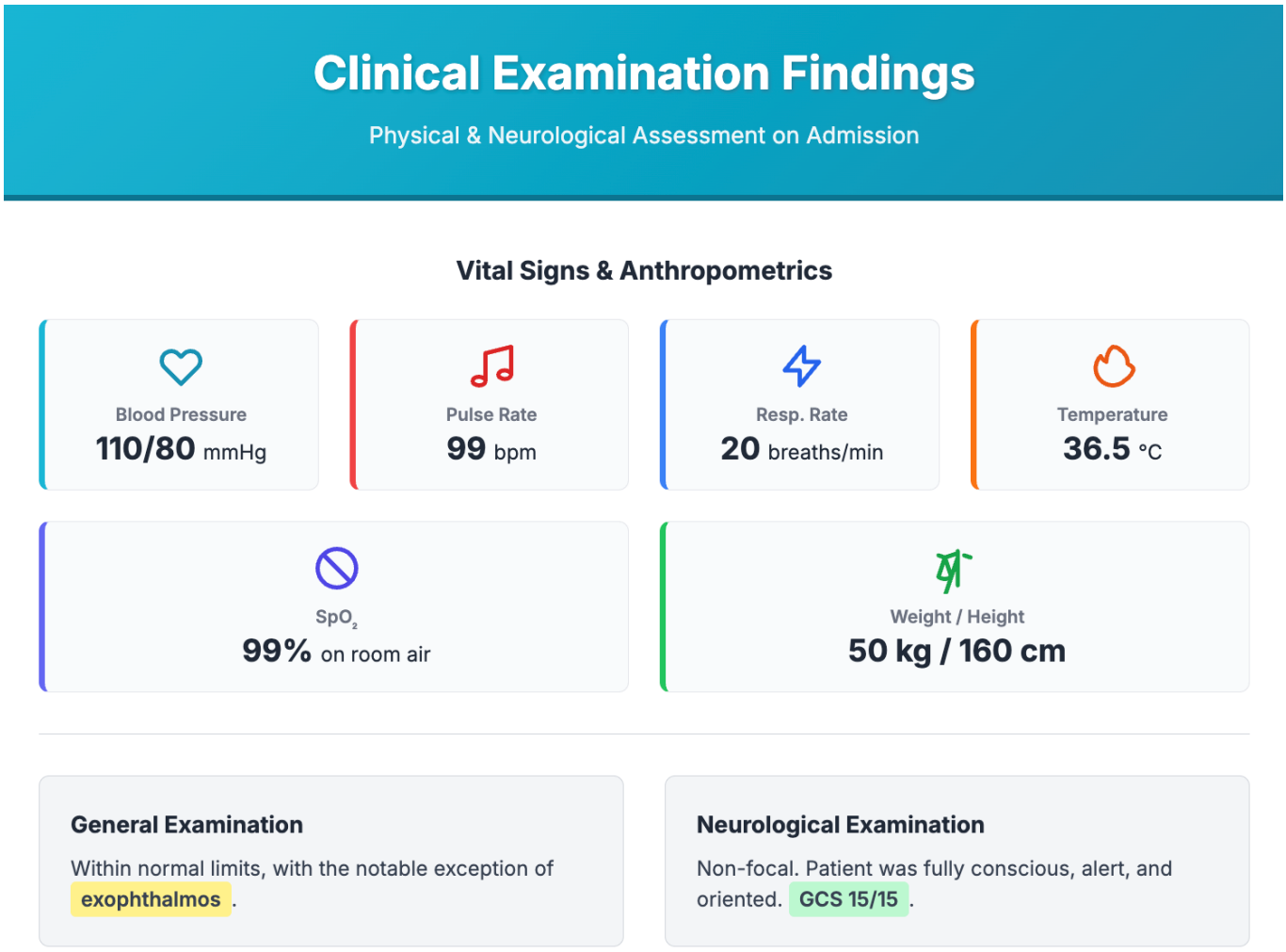

Figure 4. Physical and neurological examination findings.

The patient's mental status examination (MSE) was consistent with a severe depressive episode. She was well-groomed and cooperative but appeared visibly sad with tearful eyes. Her mood was reported as profoundly sad (hypothymic), and her affect was congruent. The most critical finding in her thought content was the presence of active suicidal ideation. While her thought process was logical and coherent, and her cognitive functions were intact, she exhibited a marked decrease in motivation (hypobulia). A detailed breakdown of the MSE findings is presented in Figure 5. The MSE, as summarized in Figure 5, formally documents the severity of the patient's depressive episode while also highlighting her preserved cognitive functions and capacity to engage in treatment.

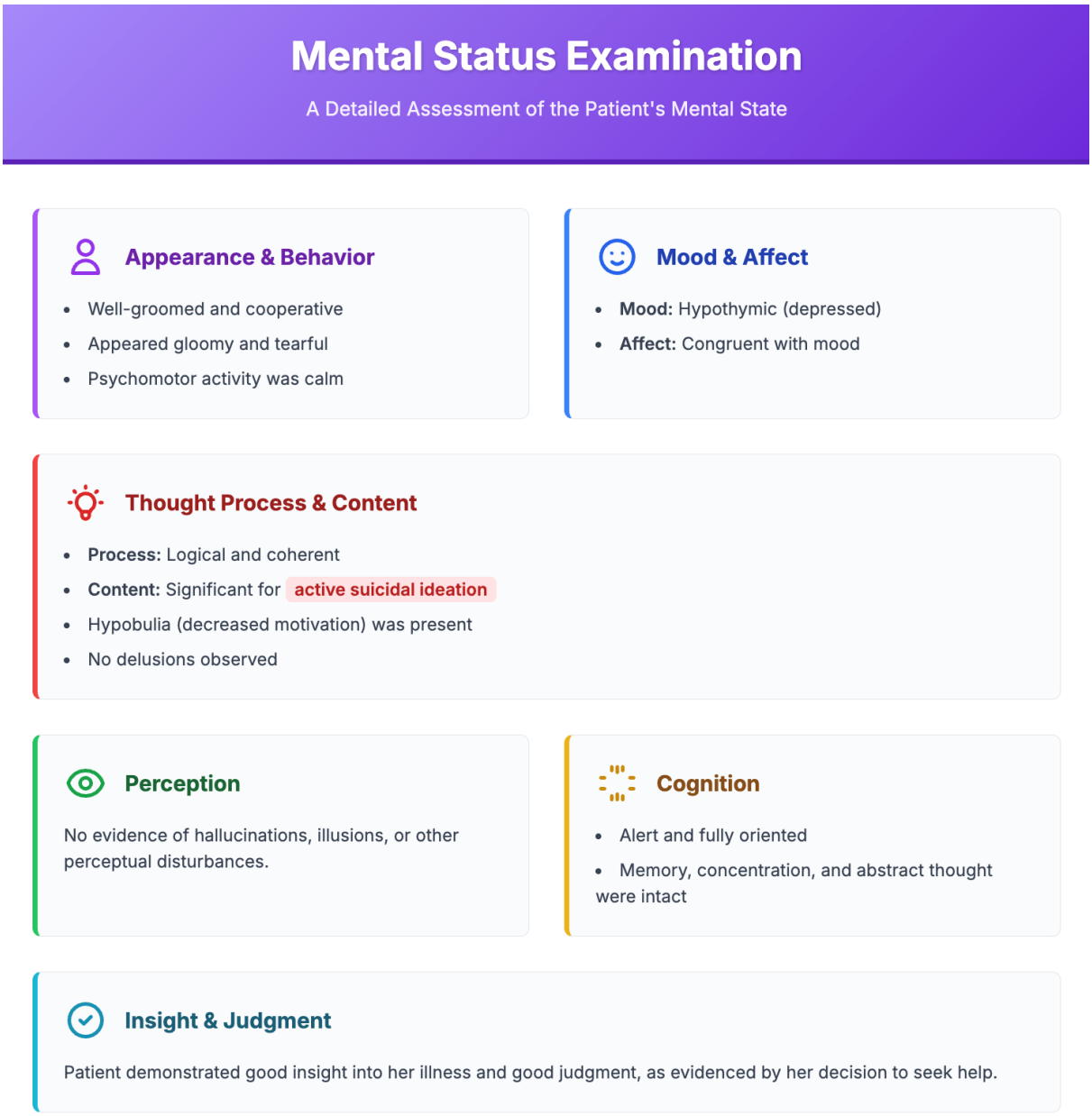

Figure 5. Mental status examination findings.

Routine laboratory investigations on admission, including a complete blood count, were unremarkable. The definitive diagnostic findings were derived from the patient's endocrine evaluation, which included thyroid imaging and serial hormone panels. The thyroid ultrasound confirmed the presence of thyroiditis. The serial thyroid function tests revealed a classic triphasic pattern of destructive thyroiditis, beginning with a phase of severe thyrotoxicosis, followed by a transient hypothyroid phase, and then a return to a euthyroid state. Thyroid autoantibodies (anti-TPO, anti-Tg) were not measured at the time of diagnosis, which represents a limitation in definitively excluding an underlying autoimmune process. The patient's serum lithium level at the time of admission was not recorded, another key limitation. The results of the key investigations are detailed in Figure 6. The data presented in Figure 6 are central to the case,

providing definitive evidence of a destructive thyroiditis. To formally assess the likelihood of a causal relationship between lithium and this adverse event, a causality assessment was performed using the Naranjo adverse drug reaction probability scale. The results of this assessment are presented in Figure 6. The total score of 6 on the Naranjo scale categorizes the adverse drug reaction as probable. This formal assessment scientifically strengthens the assertion that the destructive thyroiditis was likely caused by lithium therapy.

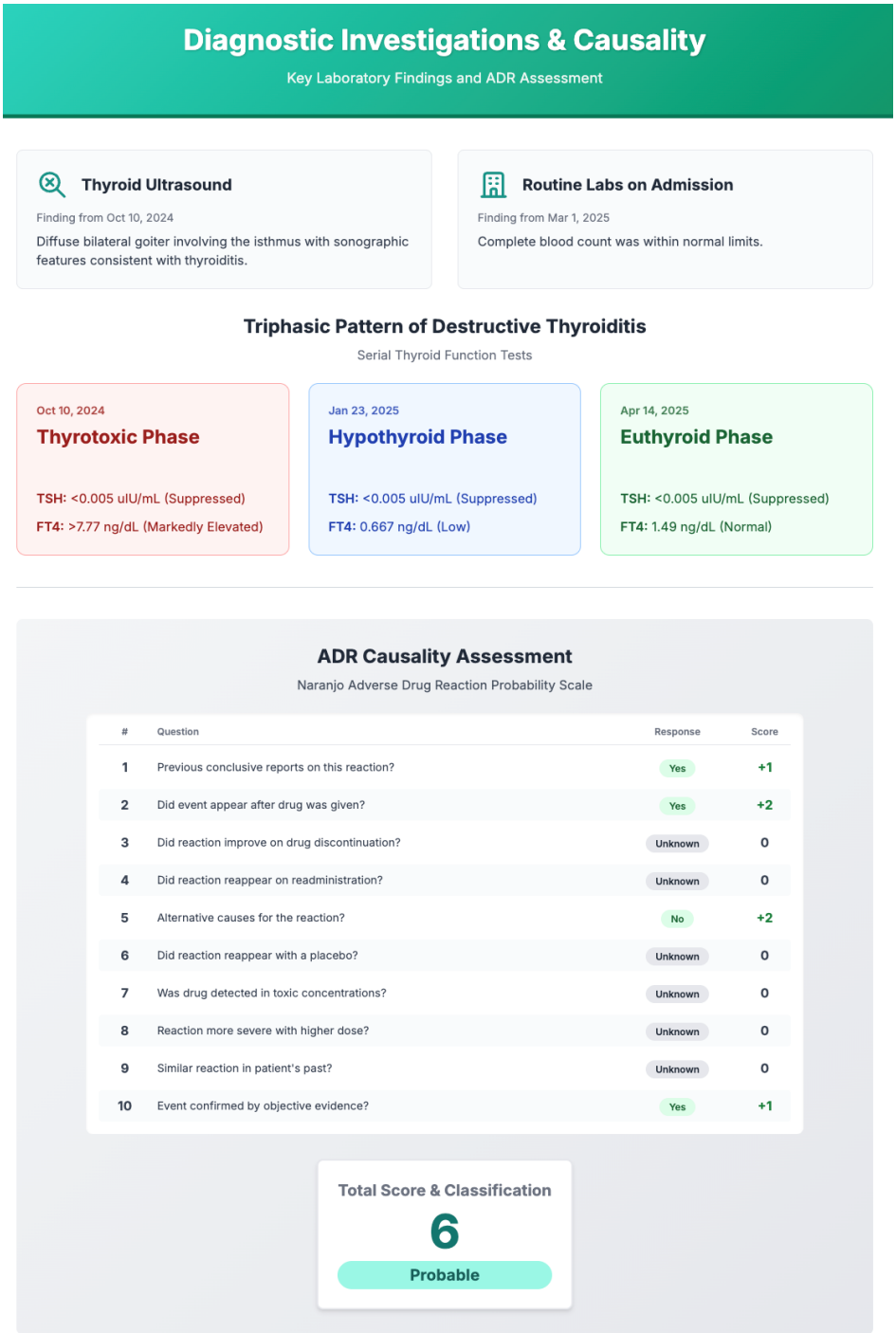

Figure 6. Diagnostic investigation findings and Naranjo adverse drug reaction probability scale assessment.

The patient was admitted to the inpatient psychiatric unit for safety monitoring and stabilization of her severe depressive episode. Her established medication regimen, including lithium, was continued. Following discharge, she was monitored closely in the outpatient setting. During a follow-up visit on July 23rd, 2025, despite the resolution of her acute suicidality, she reported persistent symptoms of irritability and social withdrawal. A key therapeutic decision was made at this point to augment her regimen with the addition of fluoxetine 20 mg daily. This intervention led to a rapid and significant improvement in her mood. A summary of her clinical course is presented in Figure 7. The clinical course detailed in Figure 7 demonstrates a complex but ultimately successful management strategy, highlighting the importance of ongoing assessment and targeted polypharmacy in addressing persistent and refractory symptoms in this dually-diagnosed patient. Informed consent was obtained from the patient for the publication of this report.

Figure 7. Clinical course, management, and follow-up.

3. Discussion

This case report details the complex clinical course of a patient with a long-standing diagnosis of Bipolar I Disorder who developed lithium-associated destructive thyroiditis, which, in a striking departure from the expected clinical presentation, manifested as a severe and progressively worsening depressive episode. The Naranjo adverse drug reaction probability scale yielded a score of 6, indicating a probable relationship between the initiation of lithium

and the onset of thyroiditis.[11] This section will, therefore, analyze the case as a probable idiosyncratic ADR to lithium therapy, focusing on the underlying pathophysiology, the diagnostic conundrum posed by the atypical presentation, and the evidence-based rationale for the clinical management decisions made. This case is of considerable clinical and scientific importance for several reasons. Firstly, it provides a detailed account of a rare but clinically significant adverse effect of lithium, a cornerstone medication in the field of psychiatry. Secondly, it highlights the profound diagnostic challenges that arise when the symptoms of a medical illness, particularly one with a known potential to mimic psychiatric states, present in an atypical or paradoxical manner. Thirdly, and perhaps most importantly, this case serves as a powerful didactic example of the intricate and often unpredictable interplay between the endocrine and central nervous systems, underscoring the absolute necessity of a comprehensive, integrated, and biopsychosocial approach to the assessment and management of patients with severe mental illness.[12]

Figure 8. Pathophysiological cascade.

Figure 8 provides a schematic representation of a complex and clinically profound pathophysiological sequence, tracing the journey from a standard psychiatric intervention to a rare and paradoxical physiological outcome. This narrative delves into the intricate mechanisms underlying the case of lithium-associated destructive thyroiditis, which, contrary to all clinical expectations, manifested not as a state of agitated mania but as a severe and life-threatening depressive episode. The cascade begins with lithium, a simple ion that has for decades served as the bedrock of maintenance therapy for Bipolar I Disorder, celebrated for its unparalleled efficacy in stabilizing mood. Yet, its use is a clinical tightrope walk, demanding constant vigilance due to a narrow therapeutic index and a significant potential for multi-system adverse effects. The thyroid gland, as this case powerfully illustrates, stands as a primary and highly susceptible target for lithium's collateral impact. The process commences with the fundamental pharmacokinetics of the drug, specifically its intrathyroidal accumulation.[13] The thyroid gland, through the sodium-iodide symporter, actively concentrates lithium to levels three to four times higher than those found in the serum. This remarkable bioaccumulation transforms the gland into a reservoir for the ion, setting the stage for significant physiological disruption. At these high intracellular concentrations, lithium interferes with nearly every stage of thyroid hormone homeostasis, from iodine uptake and organification to the synthesis and release of the active hormones, thyroxine (T4) and triiodothyronine (T3). While this interference most commonly results in goiter and hypothyroidism, a far rarer and more perplexing complication is the development of a non-autoimmune Destructive Thyroiditis.[14] This is not a case of the body's immune system mistakenly attacking the thyroid, as seen in Graves' disease or Hashimoto's thyroiditis. Instead, it is hypothesized to be a direct, sterile, cytotoxic effect of the high lithium concentrations on the thyroid follicular cells themselves. This chemical assault is thought to induce a sterile inflammatory response, leading to cellular apoptosis and necrosis, ultimately compromising the structural integrity of the thyroid follicles. The consequence of this follicular destruction is a massive, unregulated release of pre-formed T3 and T4 hormones stored within the colloid, precipitating a state of thyrotoxicosis—a systemic hypermetabolic storm.[15] This leads to the critical juncture depicted in the figure: the Resulting Clinical Presentation. The established medical literature and clinical experience prepare us for one specific outcome of thyrotoxicosis. The expected presentation is a manic-like state, a direct neuropsychiatric manifestation of the hypermetabolic condition. This classic picture is characterized by irritability, psychomotor agitation, racing thoughts (tachypsychia), anxiety, and insomnia. The phenomenological overlap with a primary manic or hypomanic episode is so profound that it creates a significant potential for diagnostic error, where a clinician might mistakenly attribute the symptoms to a psychiatric relapse and tragically increase the dose of the offending agent—lithium.[18] However, the present case diverged dramatically from this textbook expectation, revealing a paradoxical presentation of severe, functionally impairing, and actively suicidal depression. This atypical outcome demands a deeper exploration of the intricate interplay between the endocrine and central nervous systems, for which several non-mutually exclusive hypotheses have been proposed. The first, and most parsimonious, explanation is the occurrence of apathetic hyperthyroidism. This well-recognized, albeit less common, clinical variant of thyrotoxicosis is characterized by a clinical picture dominated not by hyperkinesia, but by its opposite: lethargy, apathy, social withdrawal, and profound depression, often in the absence of the typical adrenergic signs. A second, equally plausible explanation lies within the biopsychosocial model, pointing to a Potent Psychosocial Stressor. The patient was a professional

whose career was intrinsically linked to her physical appearance. The development of the disfiguring stigmata of her thyroid disease—notably significant weight loss and exophthalmos—represented a severe and highly specific psychosocial blow. The psychological impact of losing her professional identity and positive body image could have acted as a powerful, independent life event sufficient to precipitate a severe major depressive episode, an emotional response so potent that it overrode or masked any underlying physiological tendency towards agitation from the thyrotoxicosis itself. Finally, the most speculative yet neurobiologically compelling hypothesis posits a profound Neurobiological Dysregulation. Thyroid hormones are critical modulators of multiple neurotransmitter systems, including serotonin, norepinephrine, and dopamine.[16] It is conceivable that the acute, massive, and non-physiological surge of hormones during destructive thyroiditis could lead to a rapid and catastrophic dysregulation of these finely tuned systems. Rather than producing a sustained state of activation, this hormonal flood could, in a susceptible individual, lead to a rapid desensitization of key postsynaptic receptors or, alternatively, to a swift depletion of presynaptic monoamine stores due to excessively high turnover rates. Such a crash in central monoaminergic function following an initial surge would plausibly manifest clinically as a severe depressive state. This case, therefore, serves as a powerful didactic example, transforming a clinical observation into a robust scientific lesson. It challenges the monolithic understanding of thyrotoxicosis and underscores the absolute imperative for clinicians to remain vigilant for the atypical, reminding us that the same biological insult can produce vastly different clinical phenotypes, shaped by an individual's unique physiology, psychology, and life context.

Lithium has been the bedrock of maintenance therapy for bipolar disorder for more than seven decades, and its efficacy in reducing the frequency and severity of both manic and depressive episodes is unparalleled and supported by a vast body of evidence. However, its use is circumscribed by a narrow therapeutic index and a significant potential for a wide array of adverse effects, which necessitate vigilant clinical and laboratory monitoring. The thyroid gland, due to its unique physiological properties, represents a primary and highly susceptible target for lithium-induced toxicity. The mechanism for this susceptibility lies in the fact that the thyroid gland actively concentrates lithium to levels three to four times higher than those found in the serum. This intrathyroidal accumulation of lithium is known to interfere with virtually every stage of thyroid hormone homeostasis, including iodine uptake by the sodium-iodide symporter, the organification of iodine, the coupling of iodotyrosines to form T3 and T4, and the proteolytic release of these hormones from the thyroglobulin matrix. While the most widely recognized and frequently encountered thyroid-related adverse effect of chronic lithium therapy is the development of hypothyroidism, which may be clinical or subclinical and is often accompanied by the formation of a goiter, the emergence of a hyperthyroid state, particularly a thyrotoxicosis resulting from a destructive or silent thyroiditis, constitutes a much rarer, less frequently reported, and consequently, less well-understood complication.

The presumed mechanism underlying lithium-induced destructive thyroiditis is fundamentally different from that of autoimmune thyroid diseases such as Graves' disease or Hashimoto's thyroiditis. It is hypothesized to be a direct, non-autoimmune, cytotoxic effect of the high intracellular concentrations of lithium on the thyroid follicular cells themselves. This direct toxicity is thought to induce a sterile inflammatory response, leading to apoptosis or necrosis of the thyrocytes and a subsequent loss of follicular integrity.[17] This structural damage to the thyroid follicles results in an unregulated, massive release of pre-formed thyroid hormones (T3 and T4) that are stored within the colloid, leading to a state of thyrotoxicosis. The clinical presentation of

thyrotoxicosis is that of a systemic hypermetabolic state, which produces a well-known constellation of signs and symptoms, including weight loss, tachycardia, heat intolerance, tremor, anxiety, and insomnia. It is this specific symptom cluster that creates the classic diagnostic conundrum in psychiatric practice. The neuropsychiatric manifestations of thyrotoxicosis show a remarkable phenomenological overlap with the core symptoms of a manic or hypomanic episode, including irritability, psychomotor agitation, racing thoughts (tachypsychia), and a decreased need for sleep.[18] This clinical mimicry creates a significant potential for diagnostic error, wherein a clinician might mistakenly attribute the patient's emerging symptoms to a primary psychiatric relapse—a worsening of their bipolar disorder—rather than to the development of an iatrogenic medical condition. Such a misattribution could lead to the disastrous clinical decision to increase the dose of lithium, a move that would not only fail to treat the underlying condition but would also exacerbate the destructive thyroiditis and dramatically increase the risk of systemic lithium toxicity.

However, the most striking and scientifically novel feature of the present case is the profound and paradoxical nature of the patient's clinical presentation. In a complete reversal of the expected manic-like clinical picture, our patient's state of biochemically confirmed thyrotoxicosis was temporally and symptomatically accompanied by a severe, functionally impairing, and actively suicidal depressive episode. This is a highly unusual presentation that demands a detailed exploration of its potential underlying mechanisms. Several non-mutually exclusive hypotheses can be advanced to explain this paradoxical phenomenon. The first and most parsimonious explanation is that the patient experienced a form of "apathetic hyperthyroidism." This is a well-recognized, albeit less common, clinical variant of thyrotoxicosis that is more frequently described in elderly patients but can occur at any age. In contrast to the classic hyperkinetic presentation, apathetic hyperthyroidism is characterized by a clinical picture dominated by lethargy, apathy, social withdrawal, and profound depression, often in the absence of the typical adrenergic signs of thyrotoxicosis. The underlying pathophysiology of this variant is not fully understood but is thought to involve a differential sensitivity of central and peripheral tissues to thyroid hormones, or perhaps a more pronounced effect of the thyroid hormones on central serotonergic and dopaminergic pathways that mediate mood and motivation, as opposed to the noradrenergic pathways that mediate arousal and activation. A second, and equally plausible, explanation lies within the framework of the biopsychosocial model. The patient in this case was a high-functioning professional whose career and, by extension, her sense of identity and self-worth were intimately tied to her physical appearance. The development of the physical stigmata of her thyroid disease, most notably the significant weight loss and the disfiguring exophthalmos, would have represented a severe and highly specific psychosocial stressor. It is entirely plausible that the psychological impact of these changes—the loss of her professional identity, the alteration of her body image, and the perceived loss of her future—acted as a powerful, non-independent life event that precipitated a severe major depressive episode. In this model, the potent psychosocial stressor may have been sufficient to override or mask any underlying physiological tendency towards psychomotor activation from the thyrotoxicosis itself. This interpretation is supported by the patient's own attribution of her distress to her physical condition.

A third and more speculative line of reasoning delves into the complex neurobiology of mood regulation and the profound effects of thyroid hormones on central nervous system function. It is well-established that thyroid hormones are critical for the normal functioning of multiple neurotransmitter systems, including serotonin, norepinephrine, and dopamine. They are known to regulate the synthesis and degradation of these neurotransmitters and to

modulate the sensitivity of their postsynaptic receptors. It is conceivable that the acute, massive, and non-physiological surge of thyroid hormones into the circulation that occurs during a destructive thyroiditis could lead to a rapid and profound dysregulation of these finely tuned systems. Rather than producing a sustained state of activation, this hormonal surge could, in a susceptible individual, lead to a rapid desensitization of key postsynaptic receptors (such as beta-adrenergic or D2 dopamine receptors) or, alternatively, to a rapid depletion of presynaptic monoamine stores due to excessively high turnover rates. Such a "crash" in central monoaminergic function following an initial surge could plausibly manifest clinically as a severe depressive state, characterized by anergia, anhedonia, and depressed mood. This hypothesis would suggest that the temporal dynamics of the hormonal change, rather than just the absolute level of the hormone, are critical in determining the final clinical phenotype.

The clinical management of this patient required a series of nuanced and carefully considered decisions. The primary and most immediate goal upon her presentation was to ensure her safety, given the presence of active suicidal ideation. This necessitated inpatient hospitalization. The decision to continue lithium therapy in the setting of a confirmed lithium-induced thyroiditis was a complex one, requiring a careful weighing of risks and benefits. On one hand, continuing the offending agent carries the theoretical risk of prolonging or exacerbating the thyroid dysfunction. On the other hand, discontinuing lithium, which had been the cornerstone of this patient's mood stability for two years, would have exposed her to a very high and well-documented risk of relapse, particularly a potentially lethal depressive relapse. Given that the destructive thyroiditis was understood to be a transient, self-limiting condition, and given the severity of her underlying bipolar illness, the decision to continue lithium with close monitoring of both her thyroid function and serum lithium levels was a clinically sound and justifiable one. The management of her thyroiditis itself was appropriately delegated to her internist, who employed a standard and evidence-based approach with antithyroid medications to block any residual hormone synthesis and beta-blockers to manage peripheral adrenergic symptoms.

Perhaps the most critical therapeutic decision in the outpatient phase of her care was the addition of fluoxetine to her regimen. The use of antidepressant monotherapy in Bipolar I Disorder is contraindicated due to the high risk of inducing a switch into mania or hypomania.[19] However, the adjunctive use of an antidepressant in combination with a mood stabilizer is a recognized and evidence-based strategy for the management of severe or treatment-refractory bipolar depression. In this case, the patient's depressive symptoms, particularly her irritability and social withdrawal, were persistent and were causing significant functional impairment. The decision to cautiously introduce an SSRI, while continuing her mood-stabilizing regimen, was therefore a rational and appropriate one, and was ultimately validated by her rapid and robust clinical response. This positive outcome underscores the principle that even in the presence of a clear medical comorbidity, the primary psychiatric disorder must be treated assertively and according to evidence-based principles. This case provides a rich and multi-layered clinical narrative that offers numerous important lessons for the practicing clinician. It highlights a rare and atypical presentation of a known adverse drug reaction, forcing a reconsideration of the classic clinical picture of lithium-induced thyroiditis. It demonstrates the profound complexity of the relationship between the endocrine and central nervous systems and serves as a powerful illustration of the principle that the same biological insult can produce vastly different clinical phenotypes in different individuals. Most importantly, it serves as a powerful and compelling reminder that in the field of psychiatry, a thorough and ongoing consideration of underlying medical conditions is not merely an academic exercise, but an absolute clinical imperative. The art of clinical medicine often lies in the ability to recognize the atypical, to question

assumptions, and to formulate a comprehensive and integrated understanding of the patient's illness, and this case provides a masterful canvas upon which these principles are vividly displayed. This detailed analysis, structured around a formal causality assessment and an in-depth exploration of the underlying pathophysiology and clinical decision-making, aims to transform an interesting clinical observation into a scientifically robust and educationally valuable contribution to the literature. By adhering to the principles of pharmacovigilance and systematic case reporting, we hope to provide a manuscript that is not only informative but also serves as a model for the rigorous analysis of adverse drug reactions in clinical practice. The decision to continue lithium, a choice fraught with potential peril and benefit, represents the core therapeutic dilemma of this case. A thorough risk-benefit analysis is therefore warranted. The primary risk of discontinuing lithium in a patient with Bipolar I Disorder who has been stable on the medication is the exceptionally high probability of relapse. Numerous studies have demonstrated that the risk of recurrence of a mood episode, particularly a depressive one, is significantly elevated in the months following lithium cessation. For a patient with a history of severe, suicidal depression, such a relapse would be life-threatening. The primary benefit of discontinuation would be the removal of the putative offending agent, which might theoretically hasten the resolution of the thyroiditis. However, given that destructive thyroiditis is typically a self-limiting condition, the incremental benefit of discontinuation may not outweigh the profound risk of psychiatric destabilization. Conversely, the primary risk of continuing lithium is the potential for exacerbating the thyroiditis or, in a worst-case scenario, precipitating a thyroid storm, a life-threatening medical emergency. However, with appropriate endocrinological management, including the use of antithyroid medications and beta-blockers, this risk can be substantially mitigated. The benefit of continuing lithium is the maintenance of mood stability and the prevention of a potentially catastrophic psychiatric relapse.[20] In this case, the clinical team correctly judged that the risk of psychiatric relapse far outweighed the manageable risk of continuing lithium under close medical supervision. This decision is consistent with the principle of "primum non nocere," where the prevention of the most immediate and severe threat—in this case, suicide—takes precedence. Had the decision been made to discontinue lithium, several alternative pharmacotherapeutic strategies would have needed to be considered. The most logical alternative would be another first-line mood stabilizer, such as valproate or an atypical antipsychotic like quetiapine, which the patient was already taking. Valproate has a different side-effect profile than lithium and is not typically associated with thyroid dysfunction, making it a reasonable choice. Lamotrigine, while effective for the prevention of depressive episodes, is not as effective for the prevention of mania and would likely not be sufficient as a monotherapy. A combination of quetiapine and lamotrigine might be a viable option. However, any switch in medication carries its own risks, including the risk of a "discontinuation syndrome" from lithium and the time lag required to titrate a new medication to a therapeutic dose, during which the patient would be vulnerable to relapse. The decision to augment with fluoxetine in the outpatient setting was another critical juncture. As previously noted, this decision was made in the context of persistent, functionally impairing depressive symptoms. The CANMAT and ISBD guidelines of 2018 provide a framework for this decision. They recommend that for acute bipolar depression, certain atypical antipsychotics (quetiapine, lurasidone) or a combination of olanzapine and fluoxetine are first-line options. For patients who do not respond to these, adjunctive lamotrigine or adjunctive antidepressants can be considered. In this case, the patient was already on quetiapine. The addition of fluoxetine, therefore, represents a logical next step in an evidence-based treatment algorithm. The choice of fluoxetine specifically was likely pragmatic, given its long half-life and well-established efficacy in unipolar

depression. The rapid and robust response observed in this patient provides further support for the clinical utility of this strategy in select cases of treatment-refractory bipolar depression, provided that it is implemented under the umbrella of adequate mood stabilization. This case, when compared to the existing literature, stands out due to its paradoxical depressive presentation. While a handful of other case reports have described lithium-induced thyroiditis, they almost uniformly describe a clinical picture of anxiety and agitation consistent with a manic-like state. For example, the other case describes a patient who developed classic symptoms of thyrotoxicosis that were initially difficult to distinguish from an exacerbation of her bipolar disorder. This report, therefore, adds a crucial and novel dimension to the literature, suggesting that the clinical presentation of this ADR may be more heterogeneous than previously recognized. It forces us to consider the possibility that the final clinical phenotype of a thyrotoxic state is not determined solely by the absolute level of thyroid hormone, but by a complex interplay of factors, including the patient's underlying psychiatric diagnosis, their unique neurobiological sensitivities, and the psychosocial context in which the illness occurs. It is this complexity and this paradox that make the present case not merely an interesting observation, but a profound and important lesson in the art and science of clinical psychopharmacology. The meticulous documentation and systematic analysis of such cases are essential for the advancement of our understanding of the intricate and often surprising ways in which the body and mind interact. This manuscript, in its revised and expanded form, is intended to be a contribution to that ongoing process of discovery.

4. Conclusion

This case report of a 33-year-old female with Bipolar I Disorder who developed lithium-associated destructive thyroiditis with a paradoxical depressive presentation offers several critical, actionable insights for clinical practice. The primary and most salient conclusion is that the neuropsychiatric manifestations of iatrogenic thyrotoxicosis are not monolithic and can deviate significantly from the classic manic-mimicking state. The emergence of a severe depressive episode in the context of a hypermetabolic state, as detailed in this case, represents a significant diagnostic challenge and serves to broaden the recognized clinical spectrum of this rare adverse drug reaction. This case emphatically underscores the imperative for clinicians to maintain an exceptionally high index of suspicion for underlying medical etiologies, particularly iatrogenic endocrinopathies, in any patient on long-term psychotropic medication who presents with a change in mood, regardless of the polarity of that change. The successful management of this patient, which was predicated on a collaborative, multidisciplinary approach and the judicious application of evidence-based pharmacological strategies for both her endocrine and psychiatric conditions, highlights the absolute necessity of an integrated and individualized treatment paradigm. Ultimately, this report serves as a crucial reminder that a meticulous differential diagnosis and a willingness to consider and investigate atypical presentations are fundamental to the safe and effective care of patients with severe and persistent mental illness.

5. References

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