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CASE REPORTS

Combined Central Hypothyroidism and Adrenal Insufficiency Associated with Retinoic Acid Therapy for Cutaneous T-Cell Lymphoma

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Abstract

Retinoid-induced central hypothyroidism has been previously reported, but there are few reports of retinoid-associated adrenal insufficiency. Here, we present the case of a 72-year-old woman treated with isotretinoin for mycosis fungoides, who subsequently developed both central hypothyroidism and adrenal insufficiency. A 72-year-old woman with a history of mycosis fungoides was treated with isotretinoin 25 mg daily. After five months of therapy, she presented with generalized weakness, dizziness, and unexplained fainting. Thyroid-stimulating hormone (TSH) was 0.29 mIU/L (normal range: 0.4-4.5), free thyroxine (T4) was 6.1 pmol/L (normal range: 8-18), and morning cortisol was 35 nmol/L (normal range: 120-530), suggesting central hypothyroidism and adrenal insufficiency. After discontinuing isotretinoin and initiating hormone replacement therapy, both conditions showed improvement. Retinoid X-receptor (RXR) agonists like isotretinoin have been shown to suppress both TSH and ACTH secretion, leading to hypothyroidism and adrenal insufficiency. This case highlights the importance of monitoring patients on retinoids for endocrine dysfunction. Early recognition and treatment can reverse the effects.

1. Introduction

Retinoids, derivatives of vitamin A, are widely used in dermatology and oncology due to their ability to regulate cellular growth, differentiation, and apoptosis (Takahashi et al., 2022). They exert their effects primarily through retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which are expressed in many tissues, including the anterior pituitary gland. While retinoids are effective in treating conditions like acne, psoriasis, and certain cancers, including cutaneous T-cell lymphoma (CTCL) such as mycosis fungoides, they are also associated with various adverse effects, particularly on the endocrine system (Kaemmerer et al., 2021). Mycosis fungoides is a common form of CTCL, characterized by malignant T-cell proliferation in the skin (Stoll et al., 2021). Isotretinoin, an RXR agonist, has been used in its management due to its immune-modulating and anti-proliferative properties. However, isotretinoin can disrupt pituitary hormone regulation, leading to conditions like central hypothyroidism, where the thyroid gland does not produce enough hormones due to insufficient stimulation from the pituitary (Aktar et al., 2021).

While retinoid-induced central hypothyroidism is well-documented, the association between retinoids and central adrenal insufficiency is rare. Central adrenal insufficiency occurs when the pituitary fails to secrete adequate adrenocorticotropic hormone (ACTH), resulting in decreased cortisol production, which is essential for stress response, blood pressure regulation, and immune function (Martin-Grace et al., 2020). Symptoms can include fatigue, muscle weakness, and hypotension, which, if untreated, can lead to serious complications. This report presents a case of a 72-year-old woman with mycosis fungoides who developed both central hypothyroidism and adrenal insufficiency during isotretinoin therapy. The case highlights the importance of monitoring endocrine function in patients on long-term retinoid treatment and emphasizes the reversible nature of these effects with appropriate intervention.

2. Case Report

A 72-year-old female presented to the emergency department with a one-month history of progressive weakness, light-headedness, and two episodes of fainting. She was unable to stand without support and had become increasingly lethargic. The patient had a history of mycosis fungoides diagnosed seven months prior and had been undergoing treatment with isotretinoin 25 mg daily for the last

five months. Other comorbidities included well-controlled hypertension, type 2 diabetes mellitus, and hypothyroidism managed with levothyroxine (50 µg daily).

2.1. Clinical Examination

On physical examination, the patient appeared weak, with significant muscle wasting and a pale complexion. Her blood pressure was 102/50 mmHg while standing and 116/72 mmHg while supine. Her heart rate was 68 beats per minute, and there was no evidence of visual field defects, skin hyperpigmentation, or abdominal striae. A review of systems was negative for symptoms of polyuria, polydipsia, or salt craving. Further tests included an ACTH stimulation test, which showed cortisol levels of 30 nmol/L, 195 nmol/L, and 310 nmol/L at 0, 30, and 60 minutes, respectively. These results were consistent with adrenal insufficiency. An MRI of the brain was performed to rule out any structural causes of hypopituitarism, but the results were unremarkable (Table 1 & 2).

2.2. Treatment and Follow-up

The patient was initially treated with intravenous hydrocortisone (100 mg), followed by maintenance oral hydrocortisone (20 mg in the morning and 10 mg in the evening). Levothyroxine was continued at her previous dose of 50 µg daily. Isotretinoin was discontinued. After two days of therapy, her symptoms of dizziness and weakness began to improve. Four days later, hydrocortisone was held for 24 hours, and repeat testing showed an AM cortisol level of 380 nmol/L and an ACTH level of 2.1 pmol/L. The patient was discharged on thyroid hormone replacement and glucocorticoids, with instructions for follow-up with endocrinology (Table 3).

3. Discussion

Retinoids, including isotretinoin, are vitamin A derivatives that act on nuclear receptors to regulate cellular processes like growth, differentiation, and apoptosis (Comptour et al., 2016). RARs and RXRs are present in various tissues (Dawson and Xia, 2012; Kawczak et al., 2024; Ramchatesingh et al., 2022), including the anterior pituitary gland, and their activation influences hormonal signaling. While retinoid-associated central hypothyroidism has been well-documented, retinoid-induced central adrenal insufficiency remains relatively rare (Hu et al., 2020; Manna et al., 2023; Ramanarayanan et al., 2023). This case demonstrates the dual endocrine disruption caused by retinoid therapy in

Table 1: Initial laboratory results

Test	Value	Normal Range
TSH, mIU/L	0.29 (L)	0.4-4.5
Free T4, pmol/L	6.1 (L)	Aug-18
AM Cortisol, nmol/L	35 (L)	120-530
ACTH, pmol/L	N/A	1.8-14.0
FSH, IU/L	21.3 (H)	1.7-18.2
Free testosterone, nmol/L	0.72 (L)	0.9-7.3
Prolactin, µg/L	8.7	2.5-13.0
Sodium, mmol/L	134	135-145
Potassium, mmol/L	4.3	3.5-5.0

Table 2: Initial Endocrinological Workup

Hormone	Value	Normal Range
TSH, mIU/L	0.29 (L)	0.4-4.5
Free T4, pmol/L	6.1 (L)	Aug-18
AM Cortisol, nmol/L	35 (L)	120-530
Free Testosterone, nmol/L	0.72 (L)	0.9-7.3
FSH, IU/L	21.3 (H)	1.7-18.2
Prolactin, µg/L	8.7	2.5-13.0

Table 3: Thyroid and Cortisol Levels Over Time

Test	1 Week Pre-Isotretinoin	At Presentation
TSH, mIU/L	1.45	0.29 (L)
Free T4, pmol/L	13.1	6.1 (L)
AM Cortisol, nmol/L	250	35 (L)
ACTH, pmol/L	7.9	N/A

a patient with mycosis fungoides, highlighting the complex interactions between retinoid receptors and pituitary hormone regulation. The RXR receptor, to which isotretinoin binds, plays a critical role in regulating several endocrine axes (Abdelhamed et al., 2021; Brtko and Dvorak, 2020; Li et al., 2021). RXR forms heterodimers with multiple other nuclear receptors, including the thyroid hormone receptor (TR) and the vitamin D receptor (VDR). When RXR binds to its ligands, such as isotretinoin, it suppresses thyroid-stimulating hormone (TSH) by interfering with the expression of the TSH beta-subunit gene (Farasati Far et al., 2023; Thambirajah et al., 2022; Zehni et al., 2021). The activation of RXR has been shown to inhibit TSH production in the anterior pituitary by reducing the transcription of genes responsible for TSH synthesis. This mechanism was confirmed in studies involving patients receiving bexarotene, another RXR agonist, where a significant suppression of TSH and free thyroxine (T4) levels was observed (Gaunt et al., 2021). Similarly, RXR agonists can affect the hypothalamic-pituitary-adrenal (HPA) axis by reducing the secretion of adrenocorticotropic hormone (ACTH) (Egalini et al., 2022; Graceli et al., 2020). RXR has been shown to influence the proopiomelanocortin (POMC) gene, which encodes the precursor for ACTH. Retinoids, including isotretinoin, decrease the transcription of the POMC gene, leading to reduced ACTH levels, which in turn lowers cortisol production (Melnik, 2023; Pecori Giraldi et al., 2021). This reduction in cortisol levels can manifest as central adrenal insufficiency, characterized by fatigue, weakness, and orthostatic hypotension, all of which were present in this patient.

This patient's symptoms of generalized weakness, dizziness, and unexplained fainting can be attributed to both central hypothyroidism and adrenal insufficiency. The lack of peripheral edema, a common feature of primary hypothyroidism, is consistent with central hypothyroidism, where thyroid hormone deficiency arises due to insufficient stimulation from the pituitary rather than from a primary thyroid disorder. Furthermore, the patient's low blood pressure and muscle wasting are hallmark signs of adrenal insufficiency, indicating that the body's ability to produce sufficient cortisol in response to stress was compromised. Laboratory findings were consistent with both central hypothyroidism and central adrenal insufficiency. The low TSH (0.29 mIU/L) and free T4 (6.1 pmol/L) levels supported the diagnosis of central hypothyroidism. Meanwhile, the low morning cortisol level (35 nmol/L) and poor response to the ACTH stimulation test indicated central adrenal insufficiency. These findings point to an impaired pituitary function rather than a primary glandular failure. The suppression of both the thyroid and adrenal axes is consistent with the inhibitory effects of isotretinoin on RXR signaling pathways in the pituitary. The rapid improvement in this patient's symptoms after discontinuing isotretinoin and initiating hormone replacement therapy underscores the reversibility of retinoid-induced endocrine dysfunction. After the cessation of isotretinoin, the patient's thyroid and adrenal axes began to recover, as evidenced by the improvement in cortisol levels following the ACTH stimulation test. This aligns with previous reports indicating that the effects of retinoids on pituitary hormones are dose-dependent and reversible. Studies on isotretinoin and other retinoids like bexarotene have demonstrated that stopping the retinoid therapy leads to the restoration of TSH and ACTH secretion, as observed in this patient. While topical corticosteroids have been associated with mild adrenal suppression in some cases, it is unlikely that they were the primary cause of this patient's adrenal insufficiency. The patient's use of triamcinolone ointment (0.1%) was limited to localized areas and was not potent enough to induce systemic adrenal suppression. Additionally, after discontinuation of isotretinoin, the patient's adrenal function began to recover despite continued use of topical steroids. This suggests that isotretinoin was the primary culprit behind both the adrenal insufficiency and the hypothyroidism. This case represents the second reported instance of combined central hypothyroidism and adrenal insufficiency associated with isotretinoin therapy. As retinoids continue to be used in the treatment of cutaneous T-cell lymphoma and other conditions, clinicians should be aware of the potential for these medications to disrupt the endocrine system. Regular monitoring of pituitary function is crucial for early detection of hormone deficiencies, especially in patients receiving long-term or high-dose retinoid therapy. The reversible nature of retinoid-induced endocrine dysfunction also suggests that retinoid antagonists may hold potential therapeutic value in treating hypersecretory disorders of the pituitary, such as Cushing's disease. Previous studies have explored the use of RXR agonists to reduce ACTH secretion in patients with Cushing's syndrome, with some success. However, larger studies with longer follow-ups are needed to further evaluate the long-term safety and efficacy of these treatments.

4. Conclusion

This case illustrates a rare but significant adverse effect of retinoid therapy, where both central hypothyroidism and adrenal insufficiency occurred after prolonged isotretinoin use. Clinicians should maintain a high index of suspicion for endocrine dysfunction in patients receiving retinoids and ensure appropriate hormonal monitoring. The reversible nature of these effects after cessation of therapy emphasizes the importance of early intervention.

Declarations

Consent to participate

The authors declare that they have no conflict of interest

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Consent was obtained from the patient

Author contribution

S.A: Conceptualization, Investigation, Formal analysis, Writing original draft, Writing original draft, and Supervision.

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