Case Report

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

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A B S T R A C T

Background/Objective: Although retinoid-associated central hypothyroidism has been reported on several occasions, there are very few studies on retinoid-associated central adrenal insufficiency. Here, we present the case of a patient with alitretinoin-induced central hypothyroidism and adrenal insufficiency.

Case Report: An 86-year-old man with a diagnosis of cutaneous T-cell lymphoma, treated with oral alitretinoin 30 mg po daily, topical steroids, and ultraviolet light therapy presented to the emergency department with generalized weakness, decreased energy, orthostasis, and unexplained falls. Thyroid-stimulating hormone (TSH) was 0.31 mIU/L (normal range: 0.4-4.4) from 1.93 before alitretinoin therapy, whereas free thyroxine was 5.7 pmol/L (normal range: 8-18) and the AM cortisol was 40 nmol/L (normal range: 120-535); these values were suggestive of central hypothyroidism and adrenal insufficiency. Adrenocorticotropic hormone (ACTH) was not measured because of a laboratory error. Alitretinoin was stopped, and one dose of hydrocortisone 100mg IV was initiated, followed by maintenance doses of oral hydrocortisone 20mg qam and 10mg qpm. Levothyroxine (50 μg) daily was started 24 hours later. After stopping hydrocortisone for 24 hours, the AM cortisol and ACTH levels were 406 nmol/L and 2.18 pmol/L (normal range: 1.6-13.9), respectively. He was discharged on thyroid hormone replacement therapy and glucocorticoids. Repeat thyroid function tests 6 weeks later showed a TSH of 0.4 mIU/L, and free thyroxine of 9.7 pmol/L.

Discussion: Alitretinoin activates nuclear receptors called retinoic acid receptors and retinoid X-receptors. Retinoic acid receptors and retinoid X-receptors are widely expressed in the anterior pituitary gland. RXR-selective ligands such as retinoids can suppress TSH secretion, resulting in central hypothyroidism. Retinoids have also been shown to decrease ACTH secretion, which can result in central adrenal insufficiency.

Conclusion: Although central adrenal insufficiency and hypothyroidism have not been commonly reported in patients taking retinoids, they should always be considered when caring for these patients.

Abbreviations: ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; HPA, hypothalamic-pituitary-adrenal; RARs, retinoic acid receptors; RXRs, retinoid X-receptors; TSH, thyroid-stimulating hormone.

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Introduction

Retinoid-associated central hypothyroidism has been reported on several occasions but there are very few reports on retinoid-associated central adrenal insufficiency. Our objective is to present the case of an 86-year-old patient with alitretinoin-induced central hypothyroidism and adrenal insufficiency.

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Case Report

An 86-year-old man presented to the emergency department with a several-week history of progressive generalized weakness, decreased energy, orthostasis, and unexplained falls. His past medical history was significant for diagnosing Sezary syndrome (cutaneous T-cell lymphoma), treated with oral alitretinoin 30 mg po daily, topical steroids (Desoximetasone 0.25% pomade 30g, and hydrocortisone cream 1% face application twice daily as needed), and ultraviolet light therapy for the last 6 months, as well as other disorders like hypertension, atrial fibrillation, coronary artery disease, and benign prostatic hyperplasia. Other medications included Apixaban, perindopril, diltiazem, Lasix, alfuzosin, and pantoprazole.

A review of systemic characteristics revealed a stable weight, no headache or visual changes, no polyuria or polydipsia, and no salt craving. He reported mild constipation but no other gastrointestinal symptoms and also denied any other symptoms of hypopituitarism. On examination, he had a supine blood pressure of 111/69 mm Hg with a heart rate of 80 beats per minute and a standing blood pressure of 102/51 mm Hg with a heart rate of 68 beats per minute. He appeared cachectic with distal muscle wasting and weakness. There were multiple patches of erythoderma however no hyperpigmentation was observed. A head and neck examination revealed normal extraocular movements and a normal thyroid gland.

Laboratory investigations revealed chronic normocytic anemia with platelets and white blood cell count. Chemistry was within normal limits. Liver function tests were normal. Laboratory investigations showed an AM cortisol of 40 (normal range: 120-535) nmol/L, thyroid-stimulating hormone (TSH) of 0.31 (normal range: 0.4-4.4) mIU/L, free thyroxine of 5.7 (normal range: 8-18) pmol/L, suspicious for central hypothyroidism and adrenal insufficiency. A basal adrenocorticotropic hormone (ACTH) level was drawn but was unable to be processed by the lab as it was not kept on ice. A 250 μg ACTH stimulation test was performed which showed cortisol of 29 nmol/L, 241 nmol/L, and 371 nmol/L at 0, 30, and 60 minutes, respectively.

On reviewing the patient’s previous blood work, there were 2 normal TSH values 1 year and 1 week before the initiation of alitretinoin; 1.35 mIU/L and 1.93 mIU/L respectively. Three months into the treatment, TSH was noted to be low at 0.27 mIU/L (normal range: 0.4-4.4) with free thyroxine of 6.8 pmol/L (normal range: 8-18). Additional laboratory tests are presented in Table 1.

The patient was treated with one dose of 100mg of intravenous hydrocortisone, followed by maintenance doses of oral hydrocortisone 20mg qam and 10mg qpm. After 24 hours of hydrocortisone treatment, levothyroxine (50μg) po daily was initiated. On day 2, alitretinoin was discontinued. Four days later (day 6 of treatment with steroids), hydrocortisone was held for 24 hours, and blood work was repeated at 6 am that showed an AM cortisol of 406 nmol/L and ACTH of 2.18 (normal range: 1.6-13.9) pmol/L.

No testosterone replacement was administered because of his age, lower urinary tract symptoms, and history of coronary artery disease. Alitretinoin was then resumed as he was considered a candidate for other systemic therapies for cutaneous T-cell lymphoma. Hydrocortisone and levothyroxine were continued at discharge with a plan for outpatient endocrinology follow-up. Repeat thyroid function tests 6 weeks later showed a TSH at the lower limit of normal, of 0.4 mIU/L, and free thyroxine of 9.7 pmol/L (Table 2).

Discussion

Retinoids and their analogs are signaling molecules and biologically active derivatives of vitamin A. They play an important role in embryonic development, regulation of cell proliferation and differentiation, bone remodeling, and apoptosis. Mechanistically, retinoids bind to nuclear receptors called retinoic acid receptors (RARs) and retinoid X-receptors (RXRs). RXRs heterodimerize with RXR and the resultant complexes bind to the specific DNA sequences called retinoic acid response elements. Ligand binding initiates the recruitment of a series of coregulator complexes with different enzymatic activities. An immunohistological study has demonstrated that RXRs are widely expressed in the anterior pituitary gland. Additionally, RXRs also heterodimerize with vitamin D receptors, thyroid hormone receptors, peroxisome proliferator-activated receptors, and other nuclear receptors.

Central hypothyroidism resulting from using retinoids has been documented. In vitro, 9-cis-retinoic acid binds with both RAR and RXR and inhibits the activity of the TSH beta-subunit gene promoter. This process is mediated by the activation of RXR which further binds to retinoic acid response elements upstream of thyroid hormone response elements and transcription start site. Clinically, this effect has been demonstrated in a study by Sherman et al, in which patients treated with oral hexarone (selective RXR agonist) developed symptomatic central hypothyroidism. They
concluded that RXR-selective ligands can suppress TSH secretion, resulting in central hypothyroidism.\textsuperscript{5} Several other studies have also assessed the effect of isotretinoin on pituitary hormones.\textsuperscript{5-6} In a 2015 study published by Karadag et al\textsuperscript{5}, growth hormone, insulin-like growth factor-I, luteinizing hormone, follicle-stimulating hormone (FSH), estradiol, testoster-

one, sex hormone binding globulin, TSH, FT3, FT4, ACTH, cortisol, and prolactin were measured in patients receiving treatment for acne vulgaris, before the initiation of the treatment and 3 months into the treatment. After 3 months, there was a statistically significant decrease in ACTH, cortisol, insulin-like growth factor-I, growth hormone, luteinizing hormone, prolactin, total tes-
tosterone, and free T3 levels. These data are consistent with our results as the TSH and free thyroxine values reduced within 3 months into the treatment (Table 2). However, there are no published data on the long-term use of such drugs to suggest that TSH and free thyroxine might decline further.

RXR agonists have been shown to decrease proopiomelanocortin gene transcription and ACTH secretion in a dose-dependent manner.\textsuperscript{5} They also inhibit corticotroph proliferation and induce apoptosis. Given these findings, retinoids have been proposed as a potential therapy for the treatment of Cushing syndrome.\textsuperscript{7} Small clinical trials have been conducted showing a reduction in cortisol levels by retinoid treatment.\textsuperscript{8} Moreover, a study of 16 patients with Cushing syndromes such as Cushing syndrome.\textsuperscript{7} Small clinical trials have been conducted showing a reduction in cortisol levels by retinoid treatment.\textsuperscript{8} Moreover, a study of 16 patients with Cushing syndrome.\textsuperscript{7}

Table 2

| Laboratory investigations | 1 y prior | 1 wk prior | 3 mo later | 6 mo later | 6 wk duration |
|---------------------------|-----------|------------|------------|------------|--------------|
| TSH, mIU/L                | 1.35      | 1.93       | 0.27       | 0.31       | 0.4          |
| Free T4, pmol/L           | N/A       | N/A        | 6.8        | 5.7        | 9.7          |

TSH, thyroid-stimulating hormone.

It is important to note that our patient was also being treated with topical steroids of higher potency which could be a possible confounder for adrenal insuf-
ciency in most patients. Moreover, topical steroids are less likely to be the culprit as the HPA axis was restored once alitretinoin was held, despite remaining on topical steroids.

This is only the second reported case of combined central hypothyroidism and adrenal insuf-
ciency secondary to retinoids and the first associated with alitretinoin to date. This case demonstrates the importance of early and close monitoring of patients treated with systemic retinoid therapies both clinically and biochemically for evidence of pituitary dysfunction, in particular, adrenal insuf-
ciency, and hypothyroidism. Early recognition, the introduction of hormone replacement therapy, and the removal of the offending agent can lead to restoration of the HPA axis. Furthermore, the actions of retinoids can also be further investigated for the treatment of hypersecretion syndromes such as Cushing syndrome.

Disclosure

The authors have no multiplicity of interest to disclose.

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